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ELECTROPATHOLOGY OF ACUTE COR PULMONALE

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IN 1935, McGinn and White[1] described the electrocardiographic pattern of acute cor pulmonale, providing the clinician with an often pathognomonic diagnostic element. The development of lead methods afterwards permitted a number of authors to contribute with other complementary signs.[2-5]

In this paper, the electrocardiogram of experimental acute cor pulmonale is studied by means of simultaneous epicardial and intraventricular leads. The electropathology of such tracings is discussed and compared with the clinical electrocardiogram.

MATERIAL AND METHOD

Acute cor pulmonale was produced in dogs by means of mechanical compression of the pulmonary artery with an electrically isolated clamp. Isolated and simultaneous unipolar leads were recorded at different epicardial and intraventricular points before the appearance of the acute cor pulmonale, during its presence, and during its regression.

A review was made of 40 patients from the Instituto Nacional de Cardiología with the following characteristics: a definite history of pulmonary embolism, pulmonary infarction controlled by x-rays or post-mortem examination, and electrocardiograms taken before and after the embolism. Fourteen patients with pneumonia and 14 with carcinoma of the lung were also included.

RESULTS

I. Experimental Acute Cor Pulmonale

A. General Observations.—Pulmonary artery compression produced the following:

1. At the beginning, it produced dilation of the right ventricle, almost exclusively of the pulmonary conus and, later on, dilation and severe cyanosis of the right auricle.

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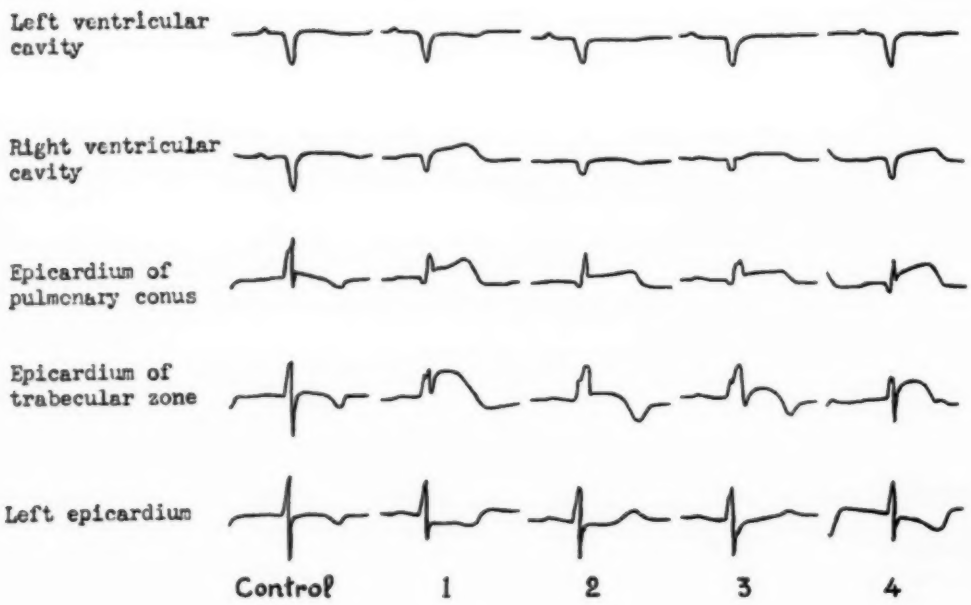
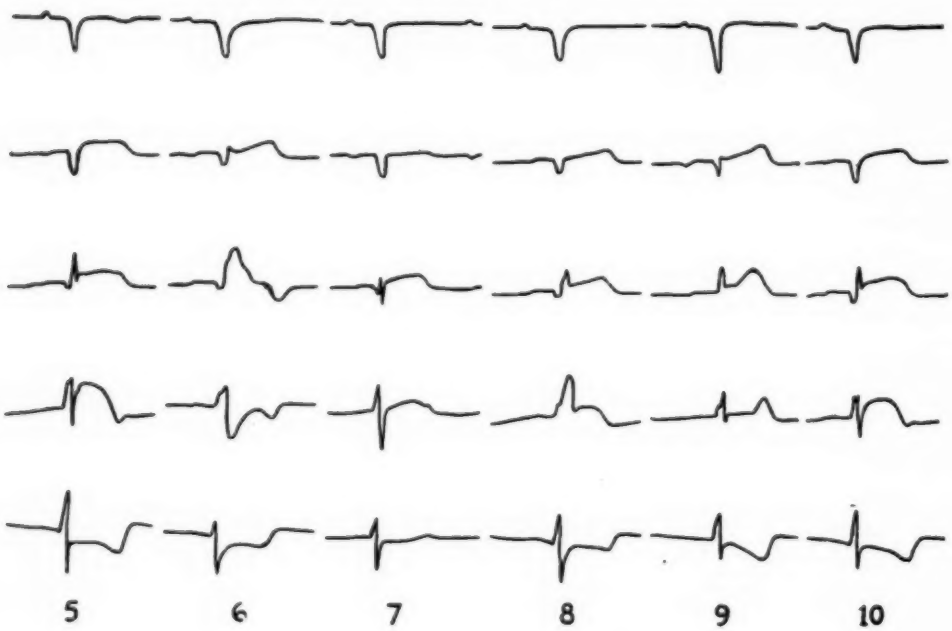


A.



B.

Fig. 1.—*A* and *B*, Unipolar simultaneous leads in different stages of acute cor pulmonale.

2. There was a decrease in the volume of the left cavities. In this case the left ventricle appeared as an appendix of the right ventricle, thus hindering the recording of the intraventricular left leads without lesion secondary to the pressure exerted by the electrode.

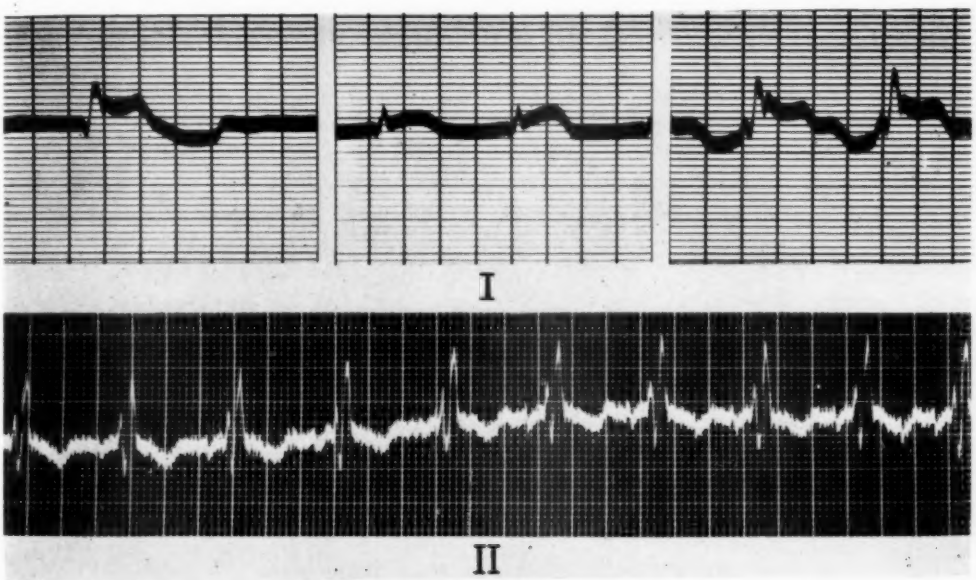


Fig. 2.—*I*, Epicardial leads of the pulmonary conus. *II*, Direct epicardial lead from the pulmonary conus of a human heart exposed by trauma.

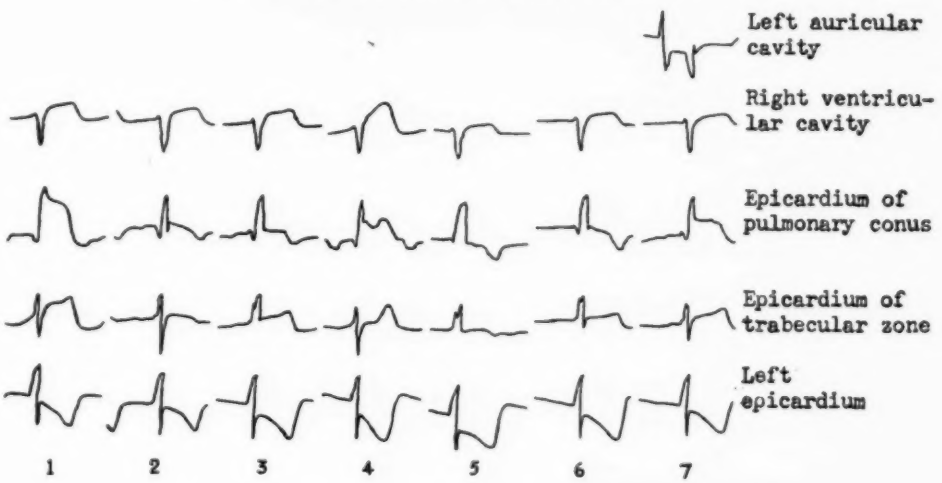


Fig. 3.—Simultaneous leads in different stages of acute cor pulmonale.

3. There was horizontal position of the heart: The right ventricle displaced the left upward and backward, thus occupying almost the whole anterior aspect of the heart, with backward rotation of the apex, often making it impossible to record the apex leads.

4. There was complete collapse of the lungs due to a decrease in the blood supply. This fact made it necessary to increase considerably the air pressure of the artificial respiration.

5. These disturbances of rhythm appeared: auricular fibrillation and flutter, which stopped spontaneously by means of the manual emptying of the auricle or the transitory removal of the pulmonary clamp, thus permitting auricular decompression; mechanical alternancy, usually combined with electrical alternancy; in more or less of 80 per cent of the experiments initial and transitory bigeminy; and atrioventricular blocks of first to third degree, reversible or irreversible.

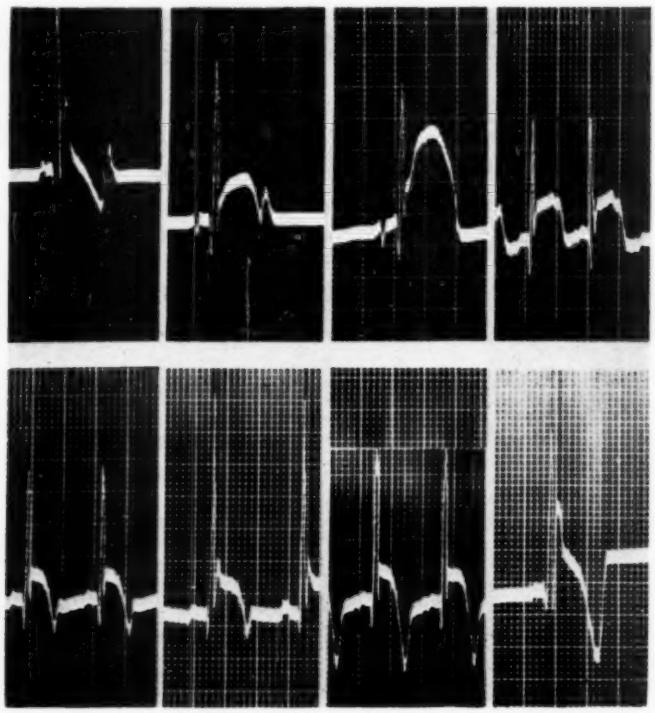


Fig. 4.—Morphology of the epicardial potential from the pulmonary conus with presence of qRs and upright RS-T.

6. The following were the causes of death, named in their order of frequency: (a) ventricular fibrillation, beginning at the interventricular sulcus (The fibrillation appeared without previous arrhythmia, sometimes with full persistency of sinus auricular activity and sometimes during the regression of the acute cor pulmonale when the clamp was removed); (b) ventricular diastolic standstill; and (c) atrioventricular block with progressively decreasing idioventricular rhythm.

B. Electrical Data.—

1. Pulmonary conus epicardium: The normal ventricular complex appeared with Rs morphology and a negative T wave (Fig. 1, *A* and *B*) and only

exceptionally showed M configuration. This last morphology could be due to a right bundle branch block previously present or produced by the introduction of the intracavitary electrode. This M complex showed a morphology similar to a tracing taken directly from the pulmonary conus of a man with the heart exposed by traumatism (Fig. 2, *II*). In this case there was right bundle branch block in both standard and precordial leads. With the acute cor pulmonale immediate and late changes appeared, and repeated compressions of the pulmonary artery were seldom needed. A positive shift of the RS-T interval of

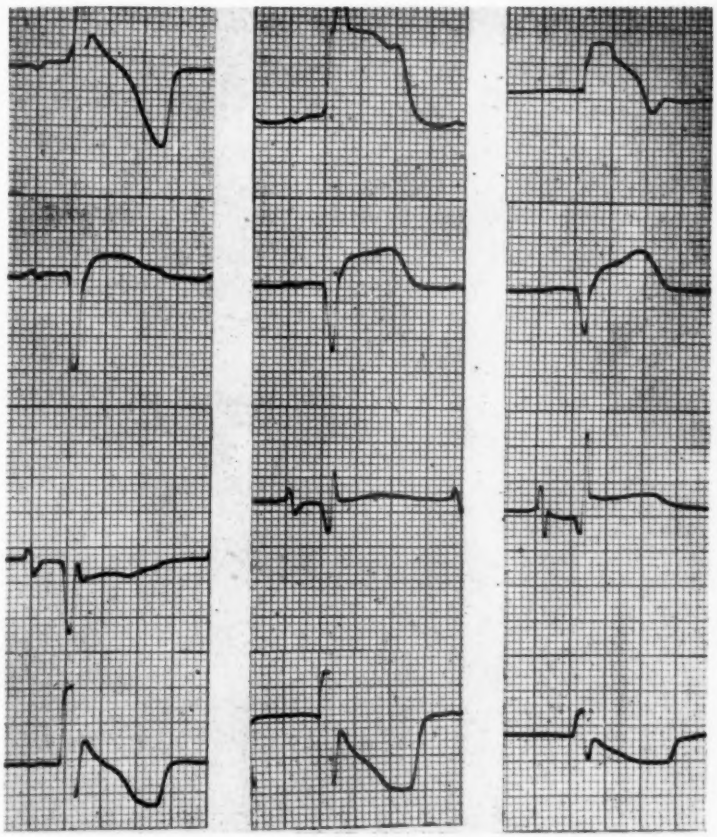


Fig. 5.—Simultaneous leads in the epicardium of the pulmonary conus, right ventricular cavity, right auricular cavity, and left ventricular epicardium.

variable magnitude was always present. The rapid complex underwent different changes: (a) a decrease of voltage, (b) the appearance of qR, which sometimes became Qr and even W (Figs. 1, 2,*I*, 3, 4, 5, and 6); and (c) the appearance of an rsR complex. When the pulmonary compression was relieved, the ventricular complex became normal, with Rs and terminal negativity of RS-T.

2. Epicardium of the trabecular zone: The normal rS complex with negative P (Fig. 1) underwent the following changes: the appearance of a second positivity, of a notch in the ascending branch of R (Figs. 1, 3, and 6), and a

positive shift of RS-T, more or less slurred as compared to that of the pulmonary conus.

3. Right ventricular cavity: The QS or rS complex showed: (a) no change, (b) low voltage, and (c) appearance of a terminal R of variable voltage. There was a positive shift of the complex RS-T, persisting for a longer time than the epicardial changes, when the acute cor pulmonale disappeared (Figs. 1, 3, 5, 6, and 7).

4. Left ventricular cavity: The normal QS complex did not show any change. The RS-T complex was depressed. (Care was always taken to avoid a positive displacement due to the pressure of the electrode.) (Figs. 1, 6, and 8,*I*.)

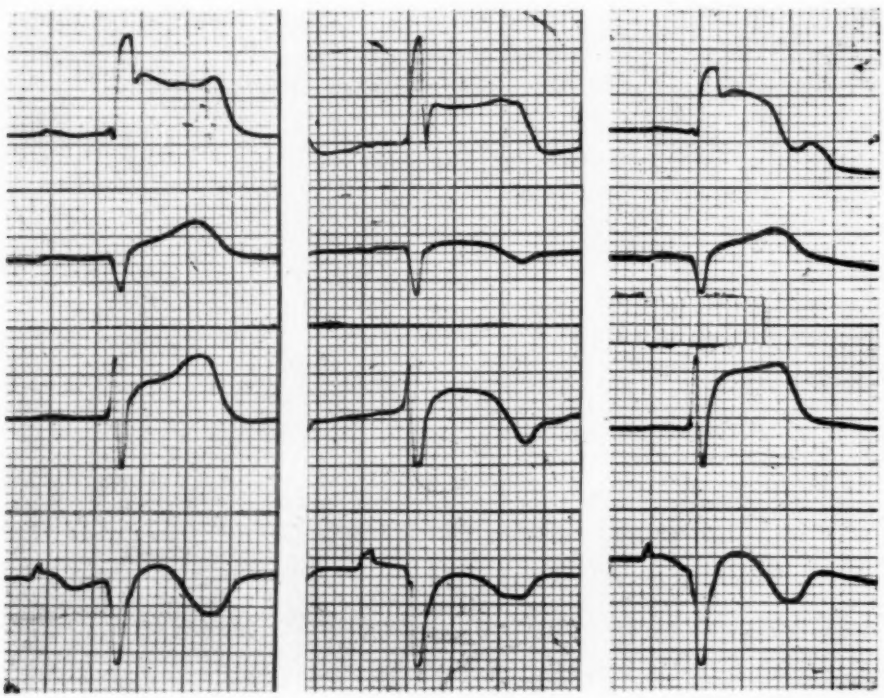


Fig. 6.—Simultaneous leads from the epicardium of the pulmonary conus, right ventricular cavity, epicardium of the trabecular zone, and the left ventricular cavity.

5. Left epicardium: The rapid qRs complex remained unchanged. There was a negative shift of the RS-T interval and, in most of the cases, the T wave became more negative (Figs. 1, 3, 5, 8,*II*, and 9).

6. Auricular cavities: There was a QR with a positive shift of RS-T in the right auricle and a QS with a depressed RS-T in the left auricle (Figs. 3, 5, and 10).

7. Simultaneous leads: From their results 4 groups can be distinguished (Figs, 1, 3, 5, 6, 9, and 11): (a) rsR in the pulmonary conus, rS in the right ventricular cavity, and rS or Rs with a slurred R in the trabecular zone; (b)

appearance of qR in the pulmonary conus with persistency of right intraventricular rS or QS, with simultaneous q and r; (c) qR in the conus with wide and notched R, in the presence of intracavitary QR or rS (there was a coincidence of the intracavitary R with the steplike notch of the ascending branch); and (d) qRS (notched R) in the conus and rSR in the cavity with simultaneous deflection, corresponding in mirror.

8. There were no modifications of the P wave in either auricular or ventricular leads.

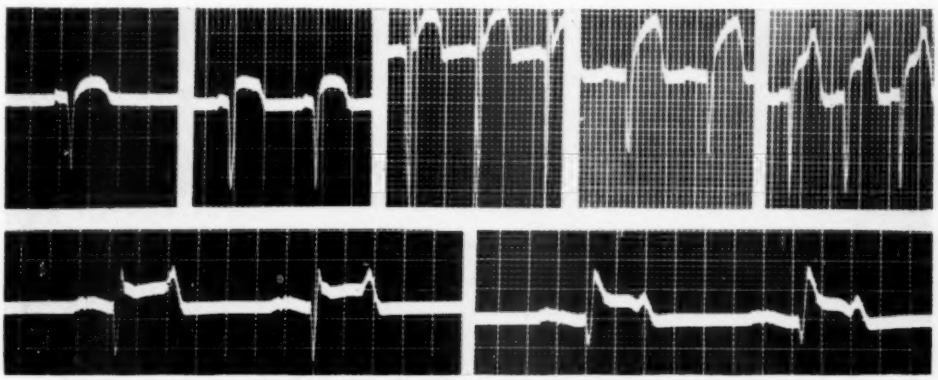


Fig. 7.—Right intraventricular leads with upright RS-T and terminal R in 3 tracings.

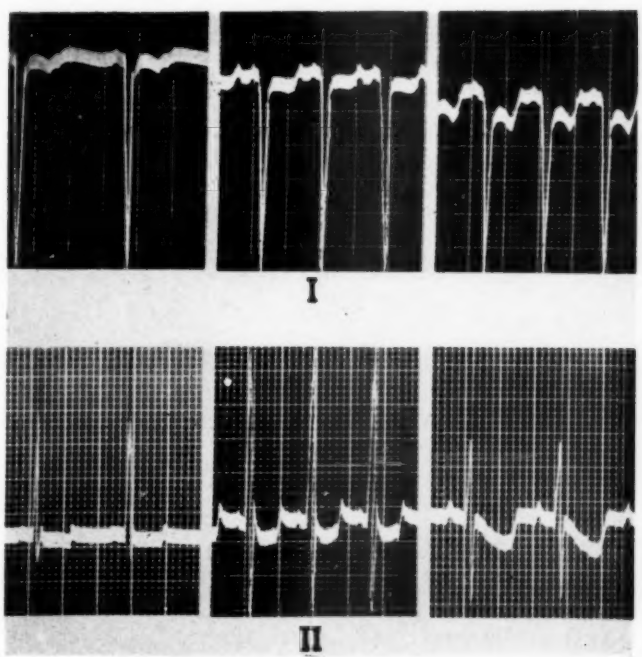


Fig. 8.—*I*, Left intraventricular potential. *II*, Left epicardial potential. RS-T is depressed in both sites.

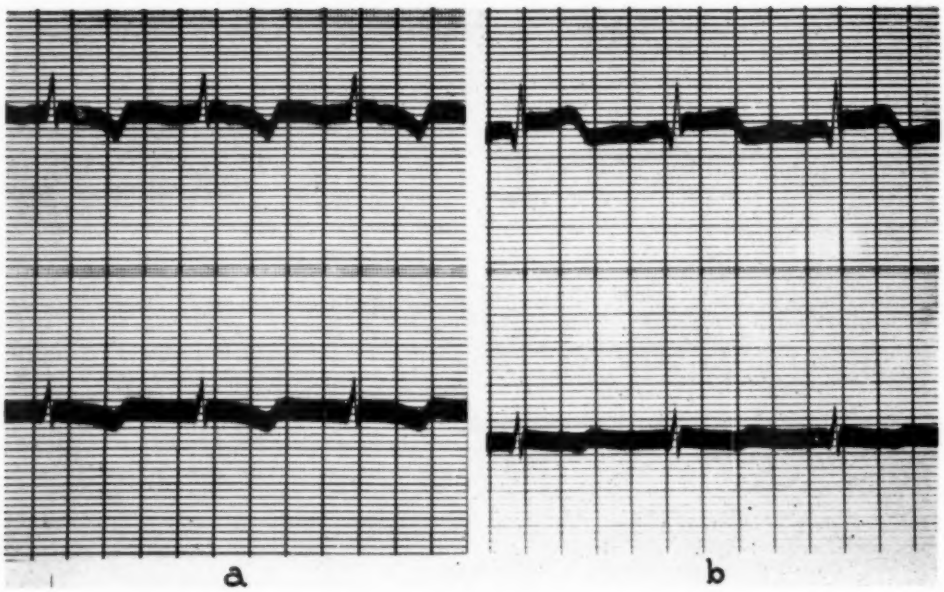


Fig. 9.—Simultaneous leads from the pulmonary conus and left epicardium before and during acute cor pulmonale.

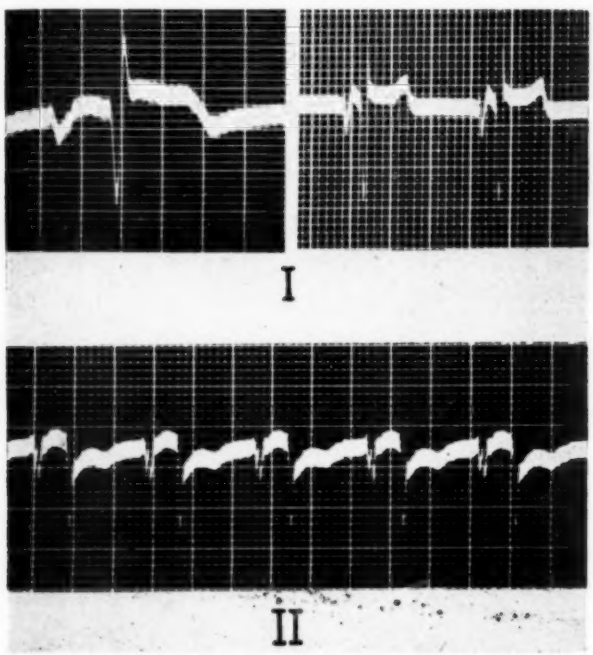


Fig. 10.—*I*, Right intra-auricular potential with QR and upright RS-T. *II*, Left intra-auricular potential with QS and depressed RS-T.

II. Clinical Cases

A. Pulmonary Infarctions.—The study of the 40 patients with serial electrocardiogram tracings permits their classification into 8 groups:

1. There were no electrocardiographic changes due to the pulmonary accidents in 15 patients (37.5 per cent).

2. There were 6 patients (15 per cent) with a shift of ÂT to the left, of $+10°$ to $-45°$. The precordial T wave was negative from V_1 to the transitional zone (V_3, V_4, or V_5). The inversion of the T wave lasted from 2 to 6 weeks.

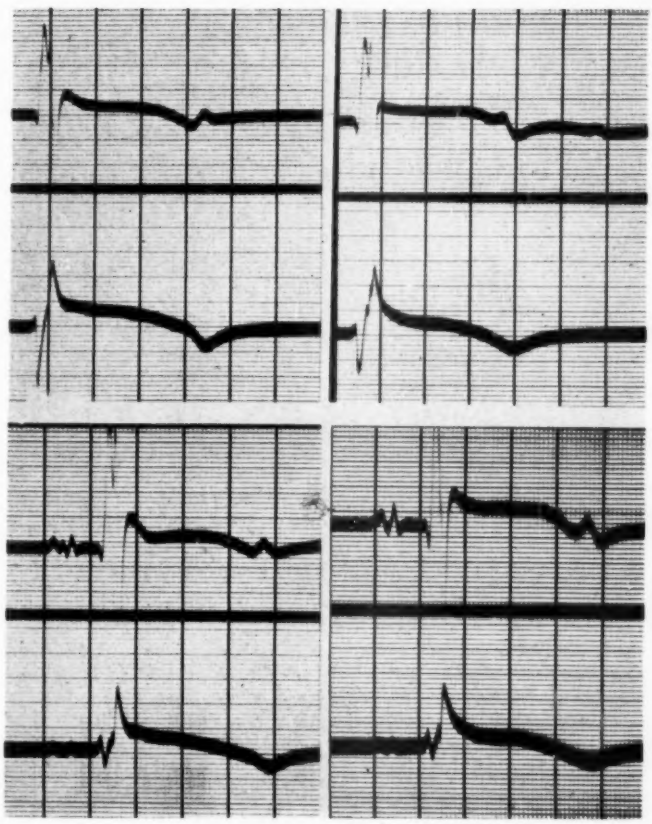


Fig. 11.—Simultaneous leads from the pulmonary conus and right cavity with QRS in the conus and a mirror tracing in the cavity, with upright RS-T in both.

3. There were 6 patients (15 per cent) with the McGinn-White pattern, with deep S_1-Q_3 in all cases. The measurements of Q_3 were 27 per cent, 37 per cent, 40 per cent, 48 per cent, 67 per cent, and 83 per cent of the maximal R in standard leads, and the measurements of Q in V_F were 4 per cent, 8 per cent, 11 per cent, and 62 per cent of R in V_F. ÂRS-T was distributed between $+150°$ and $-160°$. Therefore, RS-T was upright in 5 patients in III and in all patients in V_R. The deviation of RS-T was negative in I, II, and III in 1 patient; it was

positive in V_F in 3 patients, negative in 2, and there was no deviation in 1. A positive shift in right precordial leads and a negative one in left precordial leads were found in 2 patients. ÂT was found between +15° and −90°; therefore T_3 was negative in all patients, and T in V_F and the right precordial leads only in 4 patients (Fig. 12).

4. Disturbances of rhythm were present in 6 patients (15 per cent). Two of these patients showed auricular flutter with variable block of 2:1 to 5:1. There was another with auricular fibrillation. One patient showed infranodal rhythm and another, nodal paroxysmal tachycardia. In 1 patient with previous bradycardia of 56 per minute, there was tachycardia of 180 per minute without any other change. These disturbances lasted from 2 days to 2 weeks; only the fibrillation persisted after 2 months of the embolism.

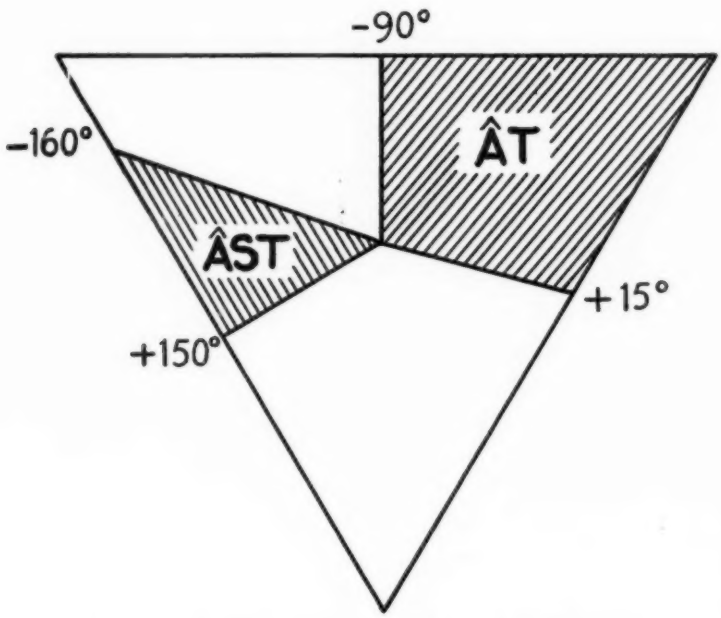


Fig. 12.—Distribution of ÂRS-T and ÂT in acute cor pulmonale.

5. A patient with previous complete left bundle branch block showed a pattern of right bundle branch block in standard leads after the embolism. Precordial leads kept their morphology of left block, thus indicating an electric vertical position of the heart. A second tracing with Q_1-S_2 and ÂQRS of + 15° changed to S_1-Q_3 with ÂQRS at +60°.

6. Two patients showed transient (5 and 8 days, respectively) rotation to the right of ÂQRS with increase of the R wave and decrease of the S wave in right precordial leads, probably as a consequence of the enlargement of the right ventricle.

7. There were 2 patients with slurring of the S wave over the right ventricle and notched R in V_1 and V_2, suggesting incomplete right bundle branch block.

8. In a patient 50 years old with arterial hypertension there was inversion of T in V_1, V_L, V_5, and V_6, corresponding to anterolateral ischemia.

9. There was no P wave with the characteristics of the P of cor pulmonale in any patient. One of them with cancer of the breast and acute cor pulmonale secondary to pulmonary embolism, whose pulmonary disease was continued by metastases, showed a P pulmonale 6 months after the first radiologic diagnosis.

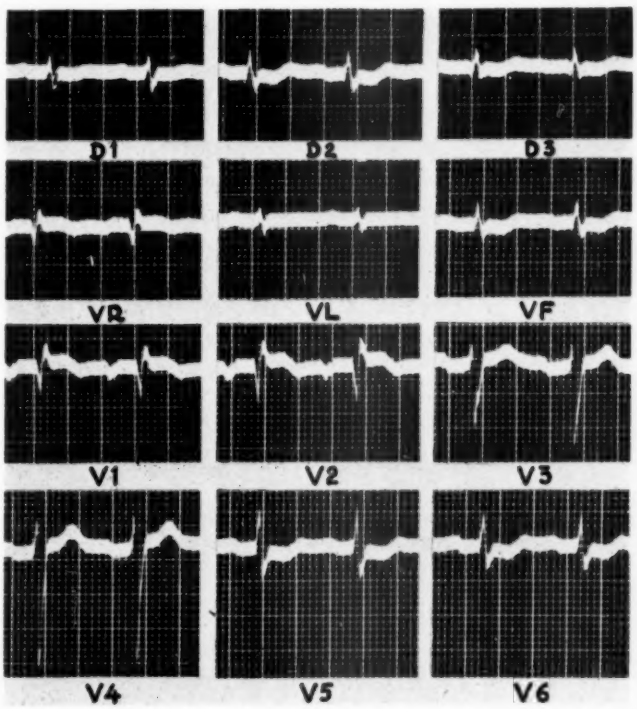


Fig. 13.—A patient with Friedländer pneumonia with a clinical diagnosis of acute cor pulmonale and post-mortem verification. There are QR and upright RS-T in V_R, V_1, and V_2.

B. Pneumonia and Cancer of the Lungs.—

1. Of the 14 patients with pneumonia (Friedländer pneumonia, 2; virus pneumonia, 1; lobar pneumonia, 5; and bronchopneumonia, 6) the first 3 showed deviation of the RS-T interval with ÂRS-T at +130°, −170°, and −120° and with ÂT at −50°, −75°, and −60°, respectively. Three patients with bronchopneumonia showed a shift of ÂT at −15°, −30°, and −45° with a negative T wave from V_1 to V_3. There were no changes in 6 of the 14 patients. The electrocardiogram of a patient with Friedländer pneumonia with a clinical diagnosis of acute cor pulmonale can be seen in Fig. 13.

2. Of the 14 patients with primary or metastatic pulmonary carcinoma 6 showed no electrical changes, 4 had a shift of ÂT at 0°, −30°, −45°, and −45°, and the other 4 had right ventricular hypertrophy, 2 of them with signs of incomplete right bundle branch block.

DISCUSSION

I. The immediate effect of compression of the pulmonary artery is an inversion of the intraventricular pressures: The left intraventricular pressure approaches 0 mm. of mercury and the right 100 mm. or more. This together with the right endocardial compression and the right myocardial distention explains the electrical picture of acute cor pulmonale without the need of introducing hypothetical reflexes.

The inversion of ventricular pressure makes the coronary circulation extremely difficult. All those factors affecting the coronary blood supply in toto, for instance, the inhalation of 10 per cent oxygen, do not produce diffuse myocardial changes but alterations limited to the most affected areas. On the other hand, the blood supply deficit due to an acute cor pulmonale involves both the left and the right networks. The gradient of pressure of both coronary arteries varies according to the pressures existing between the sinus of Valsalva and the right auricle. If these disturbances were the only consequence of the obstruction in the pulmonary circulation, the acute cor pulmonale would more frequently show pictures of left coronary insufficiency. It is a fact that left ventricular ischemias secondary to pulmonary embolism are even less frequent than the McGinn-White pattern and are only seen in old patients with coronary vessels supposedly sclerotic. It is probable that the acute cor pulmonale essentially produces, in these patients, a fall in the coronary gradient of pressure. There remains to be clarified if there is an actual inversion of the gradient; the hemodynamic conditions are in favor of such a possibility.

We may accept the fact that a diffuse coronary insufficiency plus distention of the right ventricle with unusual compression on its walls will produce a greater defect in the blood supply in the right ventricle. The electrical picture would correspond to an acute right coronary insufficiency.

Positive shifts of the RS-T interval were experimentally recorded in both the epicardium and the endocardium in both right cavities. The left heart showed an intracavitary depression of RS-T, less apparent in the epicardium. The acute cor pulmonale affects the whole right ventricle: pulmonary conus, free wall, and right septal surface. The changes recorded in the epicardium and in the cavity differ in their times of appearance and regression and in their intensities, thus indicating the presence of simultaneous wall and septal alterations. We can reject the possibility of a lesion due to the pressure of the electrode, since the shift of the RS-T complex is observed in both the right auricle and ventricle, and an auricular lesion would produce a shift of the auricular T wave. The depressions recorded from the left heart correspond to a mirror image taken at a distance from the same right lesion.

Unipolar leads used in clinical work are orientated toward the right epicardium or the right cavity when positive shifts are recorded, and toward the left epicardium or left endocardium when negative shifts are obtained. Generally speaking, in clinical cases positive shifts are registered with the unipolar lead of the right arm and in right precordial leads; the solid angle subtended by these leads involves the right heart, whether it is auricle or ventricle. The left precordial leads receive negative shifts, corresponding to the left ventricle,

and, according to the electrical position of the heart, this potential is transmitted to the left arm in patients with horizontal or semihorizontal hearts, which are the rule in acute cor pulmonale. The potential is only exceptionally transmitted to the left leg in patients with vertical hearts (Fig. 14). Accordingly, V_F may record positive or negative shifts, depending on the position of the heart. In patients with intermediate positions of the heart, the left ventricle may be transmitted to both left leg and arm (Fig. 15).

Only by exception is there a vertical electrical position with transmission of right morphology to I and V_L, as in the case of Fig. 16, where there was a dextrorotation previous to the pulmonary accident. This condition transforms the McGinn-White pattern so as to suggest a coronary more than a pulmonary accident.

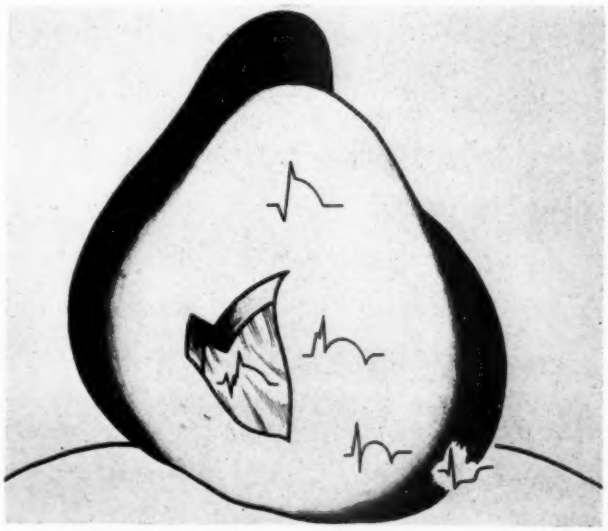


Fig. 14.—Morphology of right and left epicardial potentials and right intraventricular potential.

In 3 clinical cases of embolism, besides the electrical signs of acute cor pulmonale, there appeared positive shifts of the RS-T interval in V_5, V_6, and V_L. These patients had left lung embolism, clinically complicated with pleurisy[6] and, according to the electrical manifestation, with pleuropericarditis.

Shifts of RS-T in acute cor pulmonale are similar to those of infarction and show a rapid course toward ischemia. Thus, when pulmonary compression is relieved in experimental cases, the change shows regression, and there is ischemia in the same areas of the right heart. We have been unable to produce acute cor pulmonale by the ligature of one of the primary branches of the pulmonary artery. We think that the elimination of 50 per cent of the small circulation is not enough to produce acute cor pulmonale. Fatal acute cor pulmonale in man is observed in embolism to the pulmonary branches of third or less order, which eliminates an insignificant percentage of the circulation.

A free circulating embolus might determine a vasoconstrictor pulmonary reflex by tearing the endothelium. Such a factor does not exist in the case of pulmonary compression, and experience with thoracoplasty supports this point of view.

During regression of the lesion there appears an ischemic T in the same leads, III and V_F, which we suppose are orientated toward the posterior aspect

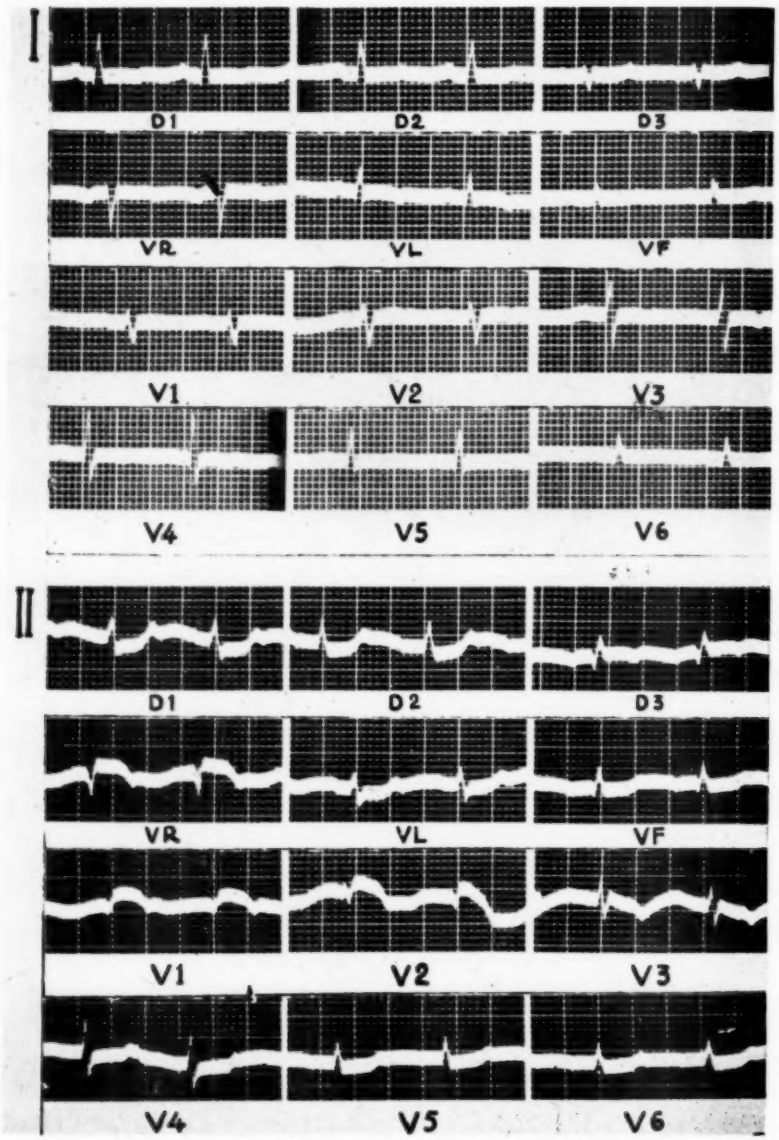


Fig. 15.—*I*, Tracing recorded 2 days before the pulmonary infarction. *II*, Seven hours after the pulmonary accident, RS-T is upright on the right ventricle and depressed on the left. The diagnosis was verified post mortem.

of the heart and right precordial leads from V_1 to the transitional zone (Fig. 17). We believe it permissible to speak about right ventricular ischemia in tracings showing a negative T in these leads. Ischemia may be due to ischemia of the free wall, the right septal surface, or both.

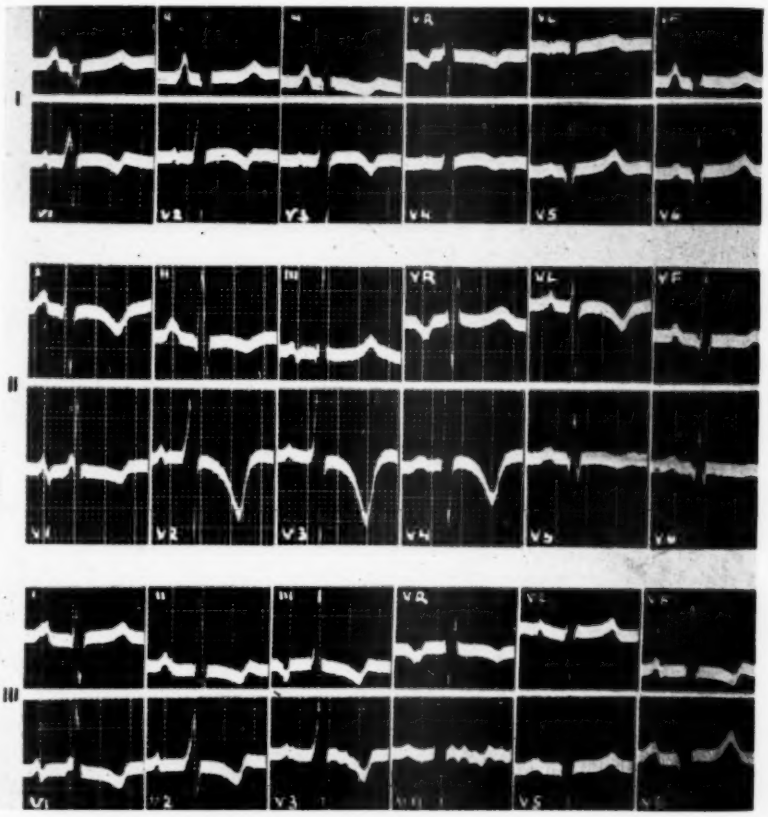


Fig. 16.—*I*, May 15, 1948, global cardiomegaly and vertical electrical position. *II*, Sept. 12, 1949, acute cor pulmonale with a greater degree of right bundle branch block and right ventricular ischemia and transmission of the negative T wave to V_L and I. *III*, Dec. 14, 1949, regression of right ventricular ischemia.

Ischemia may be consequent to an injured zone or may appear without any previous lesion. When the ischemia is accompanied by changes in the QRS complex, which will be discussed later, it speaks in favor of an acute cor pulmonale. We might use the term "subacute cor pulmonale," from the electrical point of view, to designate ischemia without QRS complex changes, which is a stage of acute cor pulmonale or which corresponds to pulmonary pathology with a subacute clinical course (pneumonia or pulmonary malignancy). The ischemia of acute cor pulmonale lasts from several days to 6 weeks or more, and the ischemia of subacute cor pulmonale may last even for several months.

ÂRS-T and ÂT show opposition in Bayley's system, thus indicating a similar origin. ÂT varies between +15° and −90°, ÂRS-T between +150° and −160° (Fig. 12).

II. Besides the characteristic signs of coronary insufficiency appearing during repolarization, acute cor pulmonale produces disturbances in the activation which may correspond to the same circulatory defect, to right ventricular hypertension, or to dilation of the cavity. These changes correspond both clinically and experimentally to different degrees of right bundle branch block. However, peculiar forms of QRS were recorded in simultaneous right epicardial and intraventricular leads in our experiments, differing from the usual morphology of right bundle branch block, discussed by Sodi-Pallares and associates.[7]

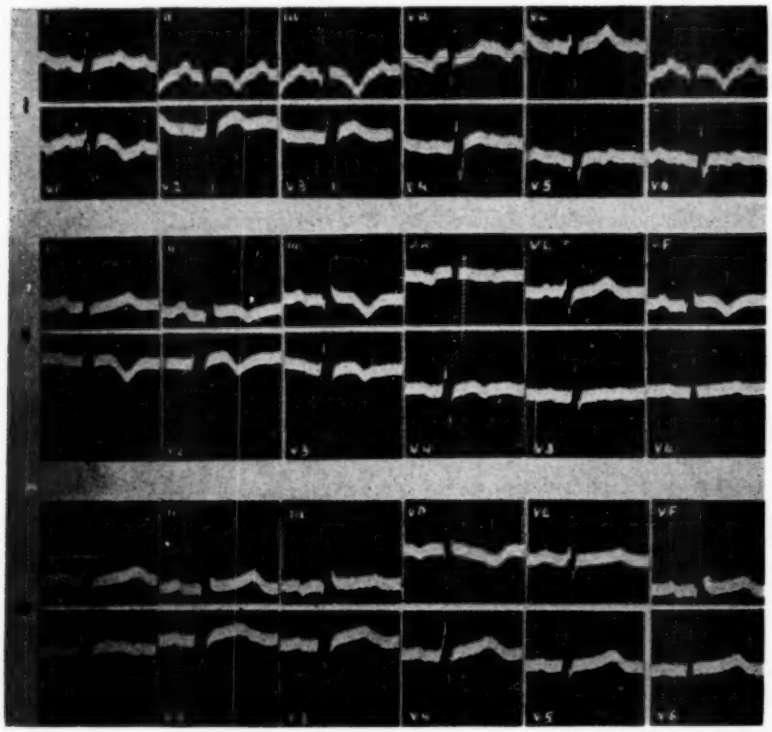
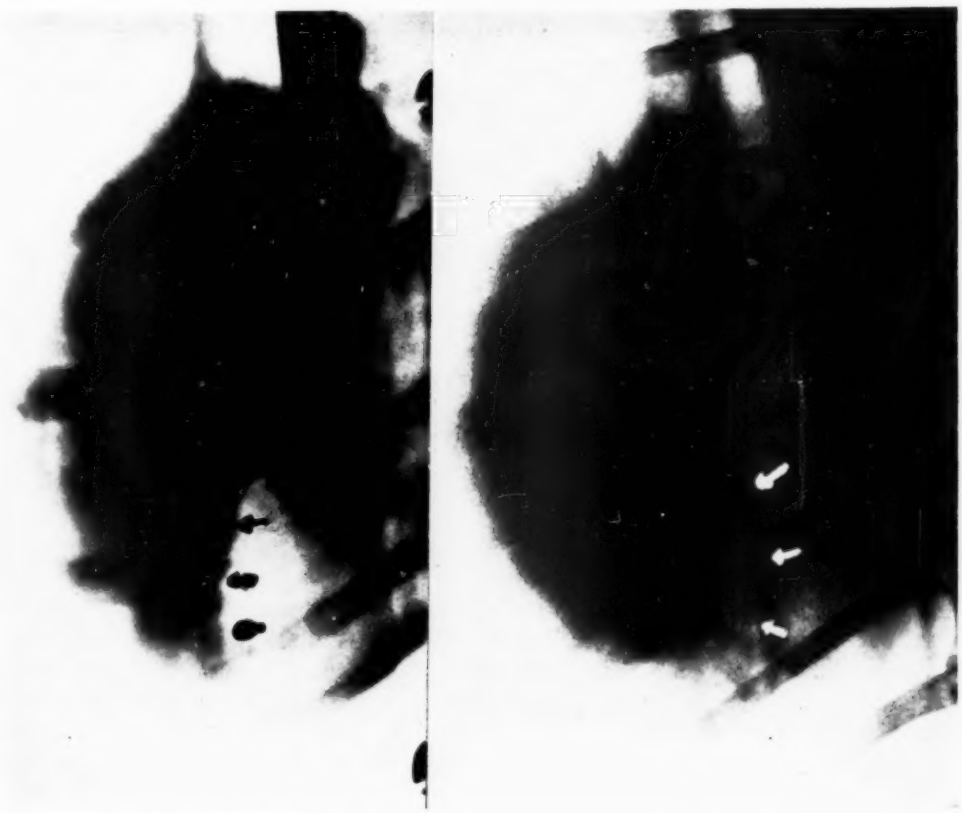


Fig. 17.—*I*, Dec. 28, 1949, first pulmonary embolism with right ventricular ischemia. *II*, Jan. 11, 1950, second pulmonary embolism with right ventricular lesion and ischemia. *III*, Feb. 15, 1950, normalization of the tracing.

An initial negativity in the epicardium of the pulmonary conus, coincident with intraventricular initial positivity, was recorded. Usually, septal vectors directed from left to right determine positivity in both sites, and vectors from the free wall will give epicardial positivity and intracavitary negativity. The intraventricular initial positivity of acute cor pulmonale must be referred to septal activation, and its simultaneous appearance with the negativity of the pulmonary conus indicates that the septal vector is going away from the conus. This zone is precisely the one undergoing greater distention, so the acute angle formed by the surface of the conus and the septum tends to open, becoming obtuse.

The intraventricular rS morphology and the qR of the conus become, with greater compression of the pulmonary artery, rsR and qRS, respectively. The

second intracavitary positivity is explained by a very delayed septal activation. The late inscription of the intrinsic deflection, coexisting with widening of the complex, is characteristic of a delay of the activation corresponding to a block, which in this particular case would be an intraseptal block. It is admitted that the process of activation is delayed in injured tissues, and that this delay increases with the intensity of the lesion, and is blocked in the limit between impaired and dead zones. The septal lesion of acute cor pulmonale would, therefore, delay the activation of the septum.



A. B.

Fig. 18.—Angiocardiography in the dog. *A*, Concavity of the septum toward the left cavity in normal state. *B*, Convexity of the septum toward the same cavity after compression of the pulmonary artery.

The right intraventricular pressure may reach such a degree that septal morphologic deformations are produced with a partial or total decrease of the septal convexity. The maximal degree of such changes, through the inversion of intraventricular pressures, may determine an "inverted Bernheim." Sussman and co-workers[8] have shown that the deviation of the septum toward the left cavity is present in some cases of chronic cor pulmonale, where the figures of right pressure are smaller than in cases of acute cor pulmonale. The angiocardiographic study of dogs with experimental acute cor pulmonale has shown that the left septal concavity may become a convexity (Fig. 18).

The "inverted Bernheim" increases the septal lesion and, at the same time, the degree of intraseptal block; it is also possible that it produces other types of changes of the activation. Contrasting with the activation of the free left ventricular wall and in spite of the similar thickness, the depolarization of the septum is manifested by a minimal deflection. This septal process takes place in a short time (till 0.02 second) and, as a consequence, the marginal vectors are partially neutralized because of their more or less opposite direction. The resulting vector would be of small magnitude, diminished also by the bidirectional septal activation.

With different degrees of "inverted Bernheim" (Fig. 19) the instantaneous septal vectors, normally diverging toward the right ventricle, become parallel with the septal leveling and may even converge when the septum presents a right concavity. The result is that the additional vector is gradually modified, being maximal when the septum is leveled.

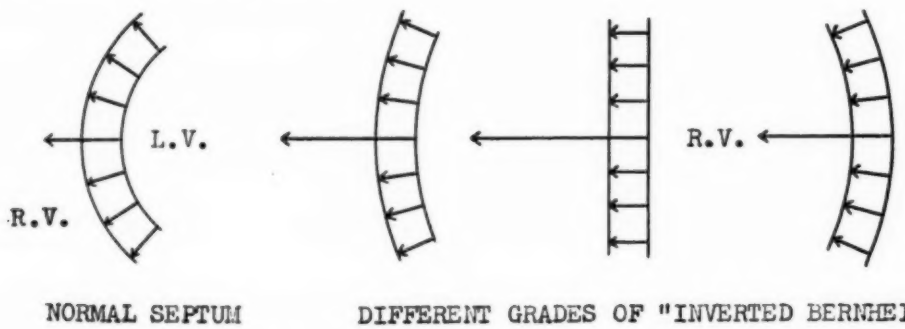


Fig. 19.—Septal activation during different degrees of "inverted Bernheim" (see text for description).

Acute cor pulmonale modifies exclusively the activation of the right ventricle. The initial positivity of the QRS complex persists in both apical and trabecular zones, while in the pulmonary conus an initial negativity may appear. It is possible to register the same type of complexes with initial negativity, sometimes in the right ventricle and, as a rule, in the right auricle. The pulmonary conus is formed by a free right anterolateral wall, the bases of the interventricular septum to the left, and a muscular structure common to the anterior aspect of the auricle in its posteroinferior portion (Fig. 20). Potentials recorded from the conus, the superior portion of the septum, and the right auricle show similar morphology, and their similarity may be explained on the basis of the already mentioned topography.

The transmission of potentials in acute cor pulmonale toward the extremities corresponds to the horizontal electrical position in the McGinn-White pattern. When there is qR in V_F, followed by a positive shift of RS-T, it corresponds to the right heart in horizontal position, but when it is followed by a negative shift of RS-T, it comes from a left potential and a vertical electrical position. The posteroinferior aspect of the heart, occupied especially by the auricles, and in acute cor pulmonale by the right auricle, transmits its potential to V_F and a Q wave of different profundity, leading to confusion with a dead zone due to

posterior infarction. Therefore, the presence of Q in V_F is not a differential sign between acute cor pulmonale and posterior infarction. With less clockwise rotation on the longitudinal axis, V_F receives apical and trabecular right potential (rS with an upright RS-T), and with rotation of the apex forward there appears a left potential (Rs, qR, both with depressed RS-T). With any type of rotation, V_R and the precordial leads will receive right heart potentials (qR to Qr, or rS, both with upright RS-T).

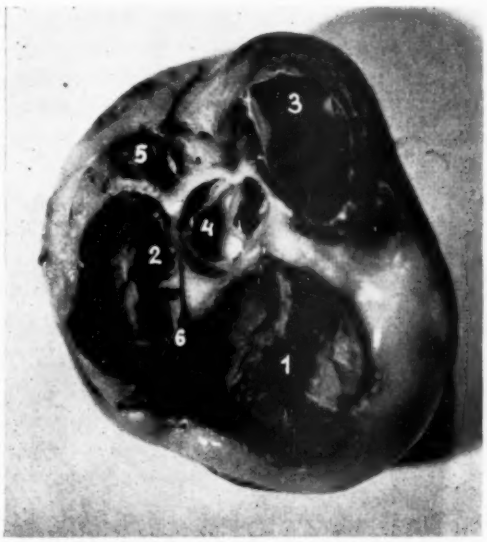


Fig. 20.—Topography of the pulmonary conus (see text for description). *1*, Right auricle; *2*, left auricle; *3*, pulmonary conus; *4*, aorta; *5*, interventricular septum; and *6*, interauricular septum.

SUMMARY

Acute cor pulmonale was experimentally produced in dogs by means of mechanical compression of the pulmonary artery.

A. General observations:

1. There was initial dilation of the right ventricle, especially of the pulmonary conus and, later on, dilation and marked cyanosis of the right auricle.

2. There was a decrease in the volume of the left ventricle, which appeared as an appendix of the right one.

3. There was horizontal position of the heart and displacement of the left ventricle upward and backward, the anterior aspect being formed in its greater portion by the right ventricle.

4. There was collapse of the lungs, which required a considerable increase in the air pressure of the artificial respiration.

5. Disturbances of rhythm appeared: auricular fibrillation and flutter, mechanical alternancy, and initial and transient bigeminy.

6. Death was due to ventricular fibrillation, which apparently began in the interventricular sulcus without previous arrhythmia, sometimes with persistency

of the normal auricular activity, diastolic ventricular standstill, or atrioventricular block with idioventricular rhythm of decreasing rhythmicity.

B. Electrocardiographic observations:

1. There appeared a positive shift of RS-T in the pulmonary conus, trabecular zone, and right cavities and a negative shift in the left epicardium and left cavities. The positive shifts of the epicardium and the right cavities appeared and disappeared independently, thus indicating the presence of 2 different lesions, one in the right surface of the interventricular septum and the other in the right wall.

2. Q appeared in the epicardium of the pulmonary conus; it was explained as due to the fact that the vector of the medial septal activation goes away from the conus as a consequence of the distention of the ejection chamber of the right ventricle. The formation of an obtuse angle between the conus and the septum follows.

3. In late stages, the right intraventricular tracing is of the rsR type, simultaneous with mirror deflections in the epicardial surface of the conus. This was explained as due to the presence of an intraseptal block, an "inverted Bernheim," and convergence and summation of the septal vector.

4. Depending on the degree of rotation of the heart on the anteroposterior axis, V_F receives left potential with RS-T depressed or right epicardial potential with upright RS-T; and, according to the rotation on the longitudinal axis, V_F registers right epicardial potential or right auricular potential with Q wave. The depth of Q in V_F is not a differential sign between acute cor pulmonale and posterior myocardial infarction.

5. Patterns simulating myocardial infarction in right precordial leads may correspond to acute cor pulmonale and depend on right cavity potentials.

6. In acute cor pulmonale coronary T waves in left precordial leads may appear; sometimes they may be its only manifestation. This may be explained by the disappearance of the gradient of pressure of the coronary circulation.

7. Positive shifts of the RS-T interval in left lateral leads (V_L, V_5, and V_6) are found in left pulmonary infarctions complicated with pleuropericarditis.

8. Generally, acute cor pulmonale determines a horizontal electrical position, only by exception a vertical one. In this last instance it shows the lesion of ischemia of the right ventricle in I and V_L.

REFERENCES

1. McGinn, S., and White, P. D.: Acute Cor Pulmonale Resulting From Pulmonary Embolism; Its Clinical Recognition, J. A. M. A. **4**:1473, 1935.
2. Love, W. S., Brugler, G. W., and Winslow. N.: Electrocardiographic Studies in Clinical and Experimental Pulmonary Embolization, Ann. Int. Med. **11**:2109, 1938.
3. Mendlowitz, M.: Experimental Pulmonary Embolism, J. Thoracic Surg. **8**:204, 1938.
4. Sokolow, M., Katz, L. N., and Muscowitz, A. W.: The Electrocardiogram in Pulmonary Embolism, Am. Heart J. **19**:166, 1940.
5. Zuckermann, R., Estandia Cano, A., Zamora, J., and Barbato, E.: Cor pulmonale agudo, Arch. Inst. cardiol. México **18**:582, 1948.
6. Aceves, Salvador: Personal communication.
7. Sodi-Pallares, D., Thomsen, P., Barbato, E., Soberón, J., Fishleder, B., and Estandía, A.: Bloqueos incompletos de rama, Arch. Inst. cardiol. México **18**:497, 1948.
8. Sussman, M. L., Steinberg, M. F., and Grishman, A.: Contrast Visualization of the Heart and Great Vessels in Emphysema, Am. J. Roentgenol. **47**:368, 1942.

ELECTROCARDIOGRAPHIC CHANGES IN PULMONARY EMBOLISM WITH SPECIAL REFERENCE TO AN EARLY AND TRANSIENT SHIFT OF THE ELECTRICAL AXIS OF THE HEART

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PULMONARY embolism is a common but often unrecognized complication of many medical and surgical conditions. Because of the difficulties often encountered in interpreting the varied clinical manifestations of pulmonary embolism, a number of investigators have studied and reported electrocardiographic abnormalities to facilitate its diagnosis. McGinn and White[1] first described the classical electrocardiographic pattern of acute cor pulmonale in pulmonary embolism. Briefly, the pattern consists of a Q wave and late inversion of the T wave in Lead III, low origin of the T wave with a staircase ascent of the RS-T segment in Lead II, a prominent S wave and slightly low origin of the T wave in Lead I, and an upright T wave in Lead IV (old method). Their study was confirmed by that of Barnes.[2] Since then, the studies of Sokolow, Katz, and Muscovitz,[3] Love and Brugler,[4] Durant, Ginsberg, and Roesler,[5] Currens,[6] Master and his associates,[7] and others[24,28,31] have contributed much to our present knowledge of the subject. As a result of these studies, other abnormalities were observed in the electrocardiograms of patients with pulmonary embolism consisting of marked RS-T segment depression in Lead I, transient intraventricular conduction delay of the right bundle branch block type, slight elevation of the RS-T segment in Lead III, inversion of the T wave in Lead CR_2, slight elevation of the RS-T segment in Lead CF_2, depression of the RS-T segments in the more lateral precordial leads, and a shift of the transitional zone to the left. It is evident that, although the classical pattern of McGinn and White is sometimes seen in patients with fairly massive pulmonary embolism, consistent electrocardiographic abnormalities diagnostic of such a condition are lacking in the majority of cases.

The purpose of this paper is to report a series of seven cases of pulmonary embolism studied with serial electrocardiograms made at various intervals from the onset of the acute attack. This study has revealed information which we feel may offer additional help in the diagnosis of relatively minor cases of pulmonary embolism. All of the patients presented acute signs and symptoms of respiratory embarrassment clinically suggestive of pulmonary embolism, and the lesions were proved by x-ray study and/or post-mortem examination. The electrocardiograms were taken with the patient recumbent or semirecumbent.

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CASE REPORTS

CASE 1.—B. M., a 37-year-old woman, was admitted to the Pennsylvania Hospital on Dec. 2, 1948 for renal calculi. Examination revealed tenderness and rigidity of the left flank and many red blood cells in the urine. A left nephrectomy was performed on Dec. 9, 1948. While sitting up for supper on December 14, she felt dizzy, short of breath, and began to cough. There was no pain in the chest. Blood pressure at that time was 100/50 mm. Hg. Oxygen, codeine, and heparin followed by Dicumarol, were given. She improved rapidly in the following fifteen hours. An electrocardiogram was taken about one and a half hours after the attack (Fig. 1,*A*), and a follow-up tracing was made fifteen hours later (Fig. 1,*B*). An x-ray examination of the chest two days afterwards showed an area of density compatible with a pulmonary infarct in the right lower lung field.

Description of the Electrocardiographic Findings.—The electrocardiogram shown in Fig. 1,*A* was obtained about one and one-half hours after the onset of the respiratory symptoms. The

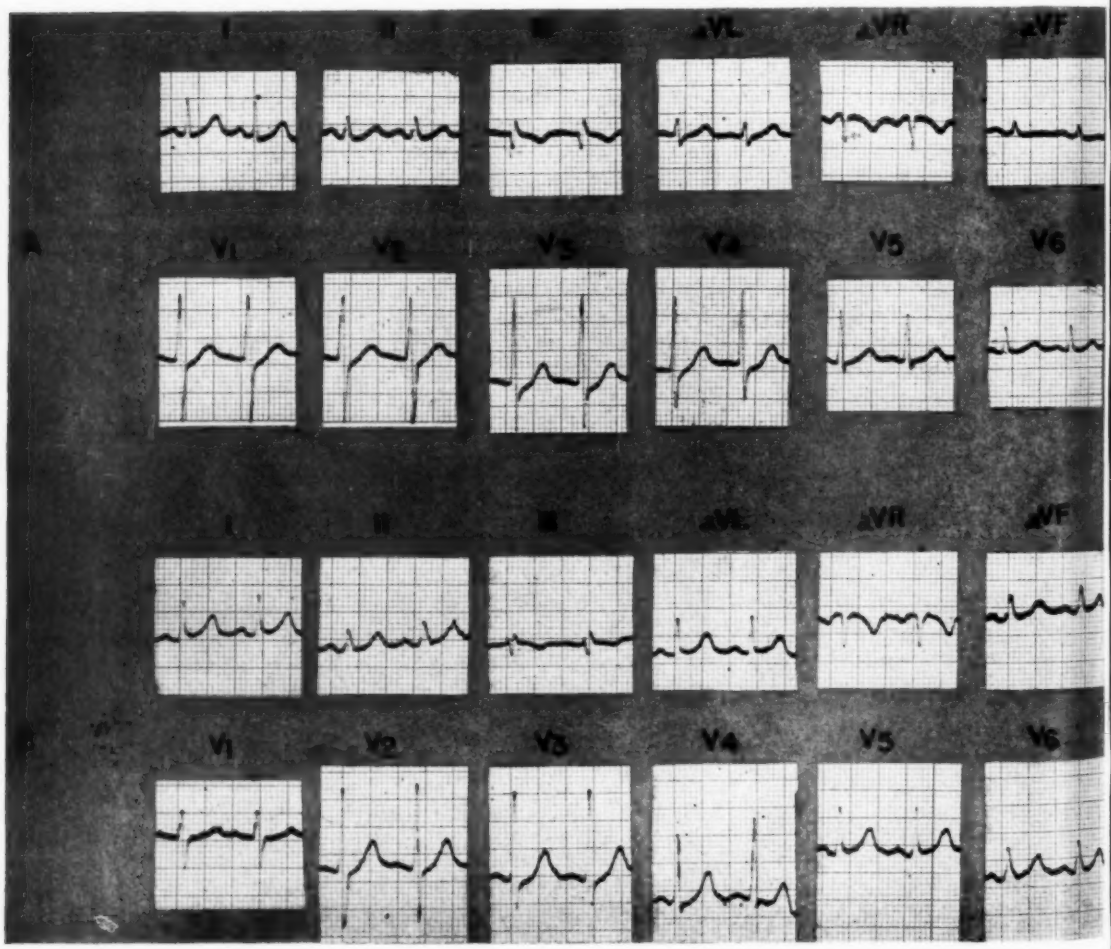

Fig. 1.—Electrocardiograms of patient B. M., a 37-year-old woman, who developed pulmonary embolism five days after a left nephrectomy. Record *A* was taken one and one-half hours after the attack and record *B* fifteen hours after *A*. For a discussion of the electrocardiographic findings see Case 1.

chief points of interest were: (1) a prominent Q wave with inverted T wave in Lead III, (2) an S wave with slight depression of the RS-T junction in Lead aV_L, (3) a mainly positive QRS complex with low amplitude of all waves in Lead aV_F, (4) S waves of various depths in Leads V_1 through V_5 and slight depression of the RS-T segments in the same leads. The electrocardiogram in Fig. 1,*B*, which was taken about fifteen hours later, showed the following changes: (1) The Q wave in Lead III had become less definite; (2) a tall R-wave pattern had appeared in aV_L; (3) the amplitude of all waves in Lead aV_F had increased; and (4) S waves had disappeared from Leads V_4 to V_6.

CASE 2.—L. H., a 50-year-old woman, was admitted to the Pennsylvania Hospital on Dec. 16, 1948, because of high blood pressure and a recent cerebral vascular accident. She had a left-sided hemiparesis. On Jan. 22, 1949, she was suddenly seized with a sharp pain in the left axilla, which was aggravated by respiratory movements. Examination showed that she was slightly dyspneic with shallow respirations at 28 per minute. The breath sounds were diminished, and a few, crepitant râles were heard over the left axilla. Her temperature rose to 101° F. and the pulse rate to 100 per minute. Her blood pressure was 125/80 mm. Hg. Signs of thrombophlebitis were noted in the left leg, and an electrocardiogram was obtained about one hour after the onset of the pleuritic pain (Fig. 2,*B*). A follow-up study was made the next morning (Fig. 2,*C*). She was treated with combined heparin and Dicumarol therapy. X-ray examination of the chest was made on Jan. 27, 1949, which showed an area of homogeneous pneumonic consolidation, triangular in shape, located in the left lower lobe of the lung. A second roentgenologic study on Feb. 4, 1949 showed a broad linear shadow in the above-mentioned area of the lung.

Description of the Electrocardiographic Findings.—A routine electrocardiogram of three standard leads and three CR leads was taken five days prior to the attack of chest pain (Fig. 2,*A*). The record showed slight left axis deviation and no abnormal changes. Approximately one hour after the occurrence of the pulmonary embolism, the electrocardiogram (Fig. 2,*B*) showed a prominent Q wave in Lead III, RS type of QRS complex with low T wave in Lead aV_L, and low R and T waves in Lead aV_F. Another electrocardiogram was taken on the next day (Fig. 2,*C*). There was no definite Q wave in Lead III, and the deep S wave in Lead aV_L had practically disappeared. The T waves had increased in amplitude throughout the limb and precordial leads. The findings were similar to those described in the previous case.

CASE 3.—A. N., a 72-year-old woman, was hospitalized on Feb. 23, 1949, because of dyspnea and loss of weight during the last six months. Physical examination revealed the patient to be disorientated. There were signs of a pleural effusion on the right side. The liver was firm and nodular. Pitting edema was present over the lower extremities but was more marked on the right than on the left side. A thoracentesis was performed on the second hospital day. The patient suddenly became dyspneic, weak, and pulseless when approximately 1,000 c.c. of pleural fluid had been withdrawn. The aspiration was immediately discontinued and the patient was put on her left side. Her condition improved, but she was weak with increased dyspnea. An electrocardiogram was taken soon after the acute respiratory distress had occurred (Fig. 3,*A*). A second record was made approximately twenty-six hours after the first (Fig. 3,*B*). The patient lapsed into coma and died on the fourth hospital day. At autopsy, the right pulmonary artery was found to be partially obstructed by an ante-mortem clot. The patient also had a bronchiogenic carcinoma of the right lung with widespread metastases.

Description of the Electrocardiographic Findings.—The record taken soon after the onset of the increased respiratory distress (Fig. 3,*A*) showed a first-degree atrioventricular heart block, a Q wave in Lead III, a prominent S wave in Lead aV_L, low R and T waves in Lead aV_F, and an RS type of QRS complex in V_2, V_4, and V_5 leads. The tracing taken twenty-six hours later (Fig. 3,*B*) showed a disappearance of the S wave in Lead aV_L, but the amplitude of the R wave in Lead aV_F had remained unchanged. S waves were not seen in the fifth precordial lead.

CASE 4.—B. D., a 70-year-old woman, was admitted to the Pennsylvania Hospital on May 15, 1949, about seventeen hours after an attack of substernal pressure and loss of consciousness. She had previously been admitted to the Women's Building on April 5, 1949 for an operation to repair a rectocele. Following her return home, she had thrombophlebitis of both legs. On admission, the patient was acutely ill. She was orthopneic and cyanotic. The neck veins were distended. There were a few crepitant râles at the base of the left lung. The heart rate was 130 per minute with regular rhythm, and the blood pressure was 98/62 mm. Hg. The right calf was tender. The first

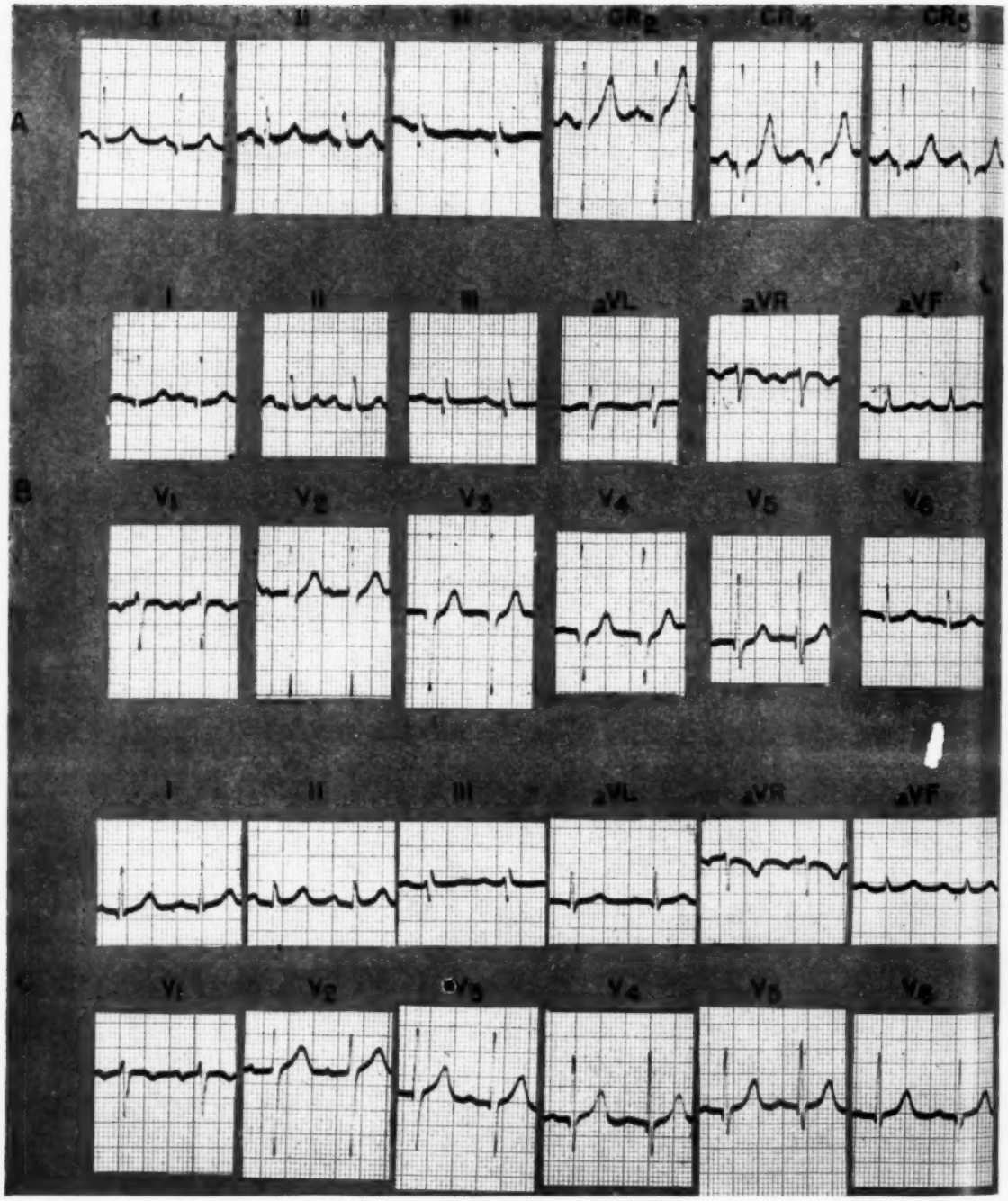

Fig. 2.—Electrocardiograms of patient L. H., a 50-year-old woman, who developed a sudden chest pain and dyspnea suggestive of pulmonary embolism following acute thrombophlebitis of the leg veins. Record *A* was taken five days prior to the onset of the chest pain. Record *B* was taken one hour after the attack and record *C* the following day. For a discussion of the electrocardiographic findings see Case 2.

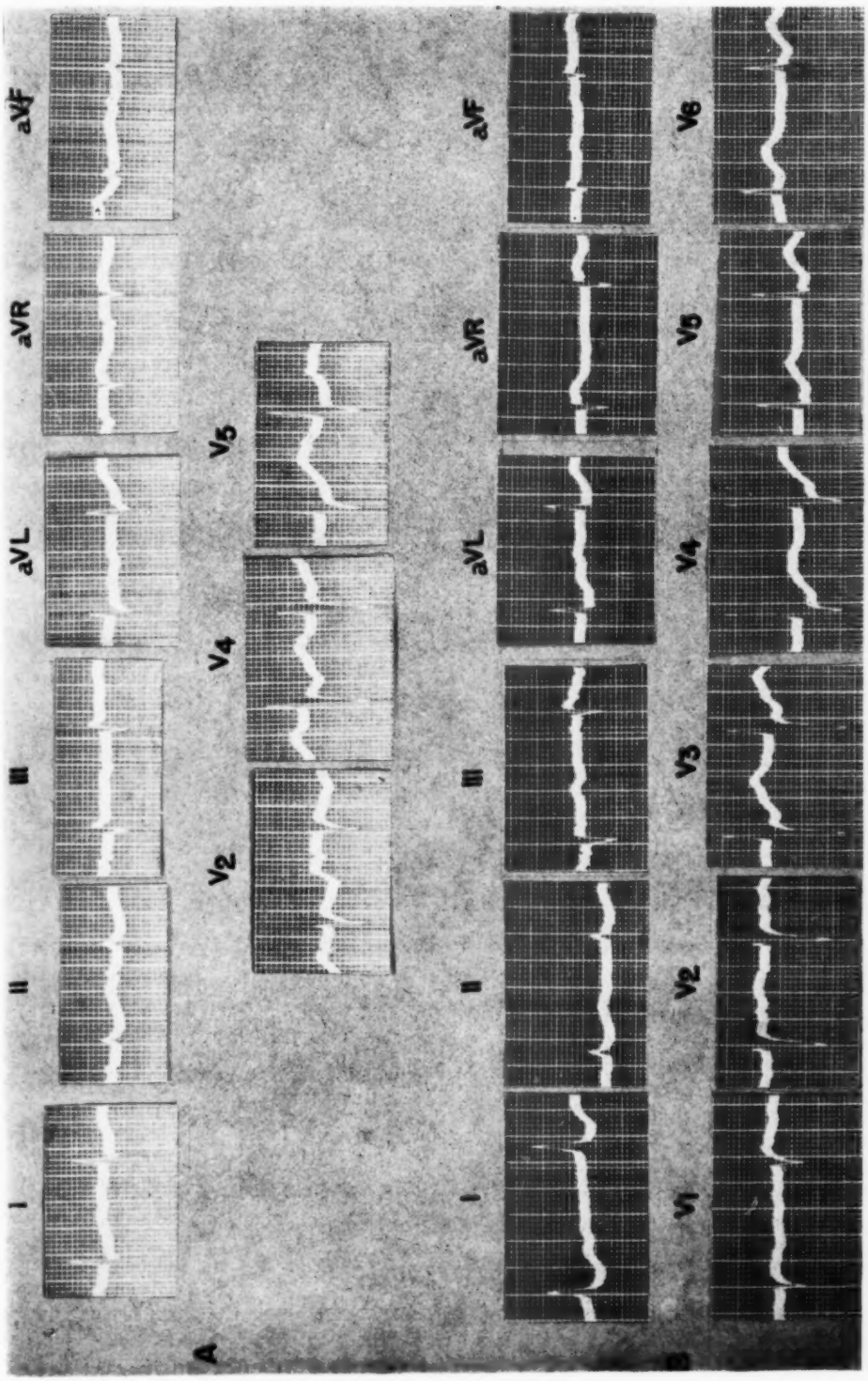

Fig. 3.—Electrocardiograms of patient A. N., a 72-year-old woman, with carcinoma of the right lung and pleural effusion in the right thoracic cavity. Record *A* was taken shortly after the onset of acute respiratory distress caused by pulmonary embolism. Record *B* was taken twenty-six hours after record *A*. For a discussion of the electrocardiographic findings see Case 3.

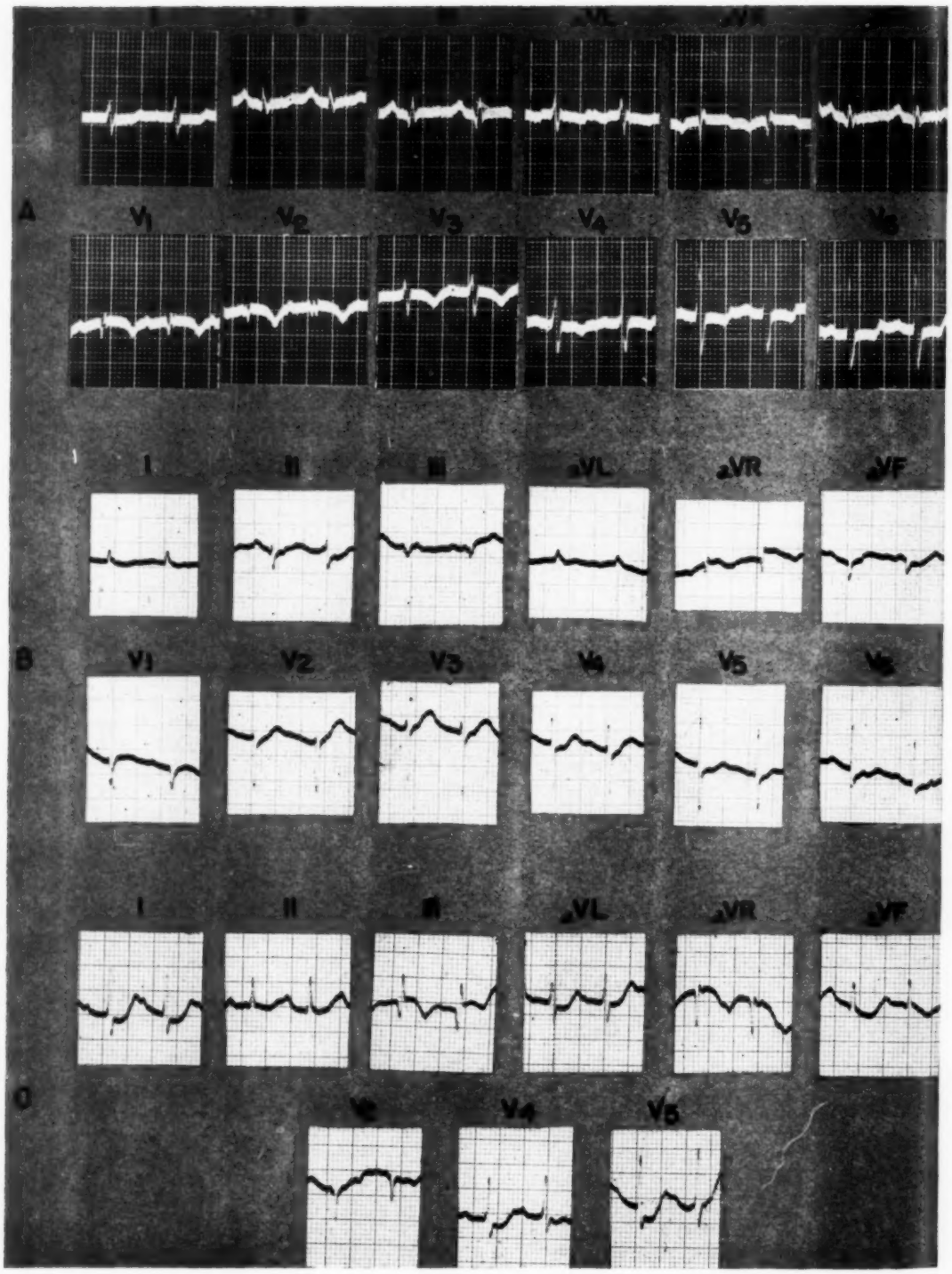

Fig. 4.—Electrocardiograms of patient B. D., a 70-year-old woman, who developed thrombophlebitis and pulmonary embolism forty days after an operation for repair of a rectocele. Record *A* was taken seventeen hours after the embolism and record *B* thirty hours after *A*. Record *C* was obtained a few hours before death from a second massive pulmonary embolism. For discussion of the electrocardiographic findings see Case 4.

electrocardiogram was made approximately eighteen hours after the acute episode (Fig. 4,*A*). An x-ray film of the chest, taken on the fourth day of the hospitalization, revealed a patch of triangular density with the apex toward the hilum in the left lower lung field. The patient was treated with anticoagulants. Daily electrocardiograms were made, and changes in the electrocardiographic findings were observed about thirty hours after admission (Fig. 4,*B*). She gradually improved and was discharged on June 25, 1949. On July 18, 1949, the patient was again seized with acute respiratory distress and collapsed. She was readmitted to the hospital in shock. The respiratory rate was 40 and the heart rate 140 per minute. The blood pressure was 90/40 mm. Hg. An electrocardiogram was taken about fourteen hours after admission (Fig. 4,*C*). The patient died a few hours later. Post-mortem examination revealed old and recent pulmonary emboli in the left and right pulmonary arteries, respectively.

Description of the Electrocardiographic Findings.—An electrocardiogram taken seventeen hours after the first pulmonary embolism (Fig. 4,*A*) showed a deep S wave in Lead I and a prominent Q wave in Lead III. There was also an RS type of QRS complex in Lead aV_L, a low R wave in Lead aV_F, and an RS type of QRS pattern in all the precordial leads. RS-T segments were depressed, and T waves were either lowered or inverted throughout the limb and chest leads. The tracing in Fig. 4,*B*, taken thirty hours after the first record, showed: (1) The S waves in Leads I, aV_L, and V_6 had disappeared; (2) the amplitude of QRS complexes and direction of T waves in the precordial leads had tended to revert to normal; and (3) the QRS pattern in Lead III had changed. However, the low amplitude of the R wave in Lead aV_F had persisted. The electrocardiogram taken shortly before the death of the patient and following a second massive pulmonary embolism (Fig. 4,*C*) was quite characteristic of the pattern of acute cor pulmonale as described by McGinn and White.[1]

CASE 5.—D. T., a 53-year-old man, had been visiting the outpatient department for eight months because of a varicose ulcer of the right leg. He came to the clinic on Sept. 30, 1948, and, as he was about to leave, he was seized with pain and a severe choking sensation in the chest. He was in collapse and was immediately hospitalized. Examination revealed great respiratory distress and shock. The blood pressure was 100/70 mm. Hg. On Oct. 1, 1948, a pericardial friction rub was heard. It disappeared in about thirty hours. Emergency treatment with respiratory stimulants, oxygen, and combined heparin and Dicumarol therapy was given. An electrocardiogram was taken within a few hours of the pulmonary accident. X-ray examination of the chest on Oct. 2, 1948 revealed a patch of localized pneumonitis at the right base. The patient responded satisfactorily and was discharged on the twenty-fourth hospital day.

Description of the Electrocardiographic Findings.—The first electrocardiogram (Fig. 5,*A*), which was taken within a few hours of the pulmonary embolism, was quite characteristic of the acute cor pulmonale pattern. A slight intraventricular conduction delay of the right bundle branch block type was also present. The second record, made about twenty-four hours after the first one (Fig. 5,*B*), showed an inversion or lowering of the T waves from V_1 through V_4. The T waves were of fairly good amplitude in Leads V_5 and V_6. The patient had made a good clinical recovery from the pulmonary insult when the last record was made (Fig. 5,*C*). The record showed a left axis deviation and was within the limits of normal.

CASE 6.—P. F., an 82-year-old man, was admitted to the Pennsylvania Hospital on Nov. 28, 1948, with a history of fainting suddenly and falling on the stump of his right leg amputated at the thigh. He was known to have arteriosclerotic heart disease and mild congestive failure. On admission, he was found to be cyanotic, orthopneic, and drenched with cold sweat. There were many wheezing inspiratory râles heard throughout both lung fields, and moist râles were present at the left lung base. The heart rate was approximately 120 per minute with a totally irregular rhythm. The blood pressure was 70/50 mm. Hg. The first electrocardiogram was taken about six hours after the fainting spell, and a second record was taken twelve hours after the first one. Roentgenologic examination of the chest on the second day of admission revealed a large area of increased radiability of the right lower lobe, consistent with an acute occlusion of a pulmonary artery. The lung fields became homogeneous in density radiologically on a second film study ten days later. The patient responded well to digitalis and anticoagulant therapy and was discharged from the hospital on the twenty-fifth hospital day.

Description of the Electrocardiographic Findings.—The electrocardiogram made approximately six hours after the fainting spell (Fig. 6,*A*) showed auricular fibrillation, a slight degree of intraventricular conduction delay, and the pattern of acute cor pulmonale. Normal sinus rhythm had returned when the second record was made (Fig. 6,*B*). The depressed RS-T segments and the lowered T waves seen in Fig. 6,*B* were probably related to digitalis therapy. The electrocardio-

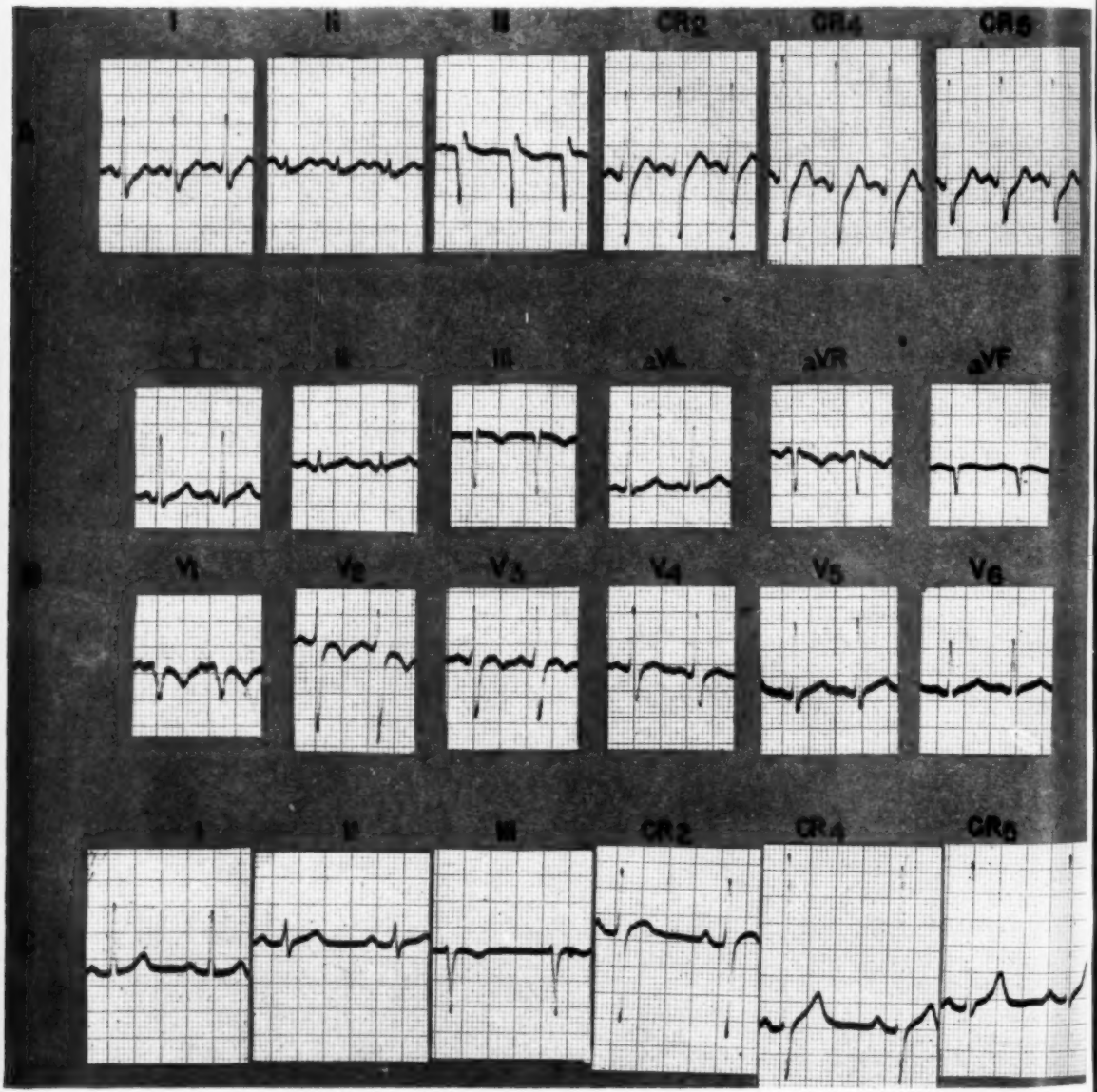

Fig. 5.—Electrocardiograms of patient D. T., a 53-year-old man, who suffered from varicose ulcers of the legs. He had an attack of pulmonary embolism while visiting the surgical peripheral vascular clinic. Record *A* was taken a few hours after the attack and record *B* twenty-four hours after *A*. Record *C* was taken after the patient had recovered from the pulmonary accident. For discussion of the electrocardiographic findings see Case 5.

gram seen in Fig. 6,*C*, which was taken two weeks after the acute pulmonary episode, was normal with left axis deviation and digitalis effect.

CASE 7.—E. W., a 62-year-old woman, was admitted to the Pennsylvania Hospital on Nov. 1, 1948 because of intestinal obstruction. A supravaginal hysterectomy had been performed in 1942 for carcinoma of the cervix. The intestinal obstruction was found to be caused by widespread metastases of carcinoma involving the intestines and pelvic organs. A palliative cecostomy was performed on Nov. 11, 1948. In the evening of Dec. 3, 1948, she suddenly became dyspneic and went into profound shock. Her pulse was small, rapid, and irregular. Blood pressure was 66/56 mm. Hg. An electrocardiogram was taken about three hours after the onset of the severe respiratory embarrassment, and a second one was obtained the next morning. The patient did not respond to cardiac and respiratory stimulants and lapsed into coma and died. Autopsy showed multiple large emboli of tumor cells and blood clots in the main branches of the pulmonary arteries.

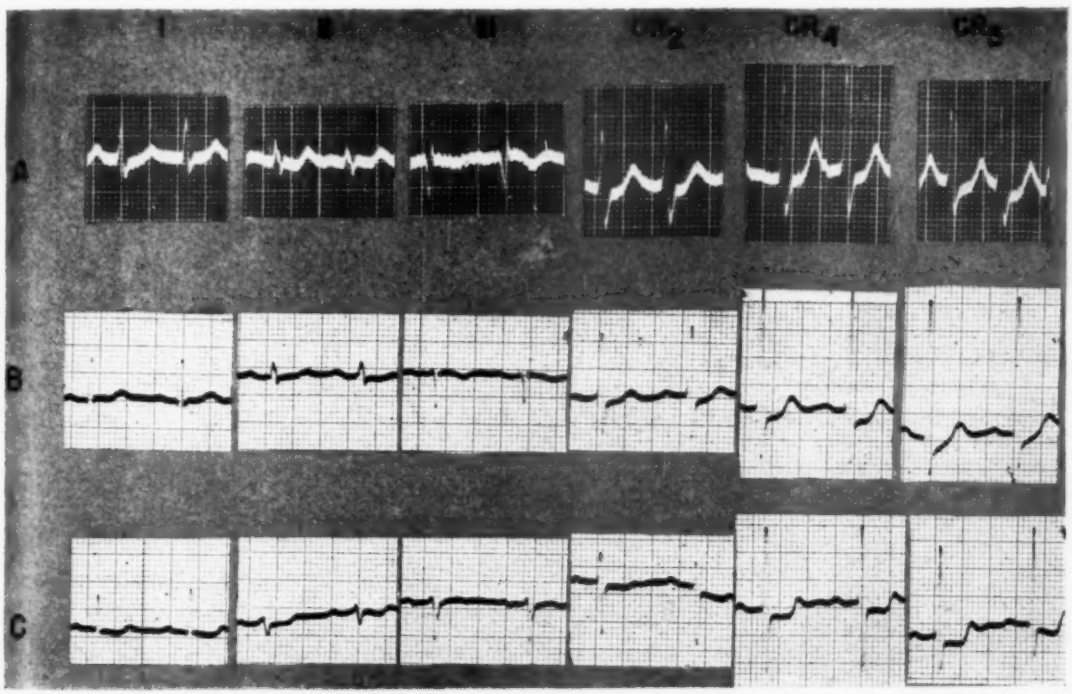

Fig. 6.—Electrocardiograms of patient P. F., an 82-year-old man, who developed symptoms of acute respiratory distress suggestive of pulmonary embolism following a fall on the stump of his right leg amputated at the femur. Record *A* was taken about six hours after the attack and record *B* twelve hours after *A*. Record *C* was taken two weeks later. For discussion of electrocardiographic findings see Case 6.

Description of the Electrocardiographic Findings.—A routine electrocardiogram (Fig. 7,*A*), taken on Nov. 11, 1948 before the attack of pulmonary embolism, was normal with left axis deviation. The patient was in severe respiratory distress and shock when the second record was taken on Dec. 3, 1948 (Fig. 7,*B*). It showed auricular fibrillation and an acute cor pulmonale pattern with slight intraventricular conduction delay. There was also a generalized lowering of the amplitude of all waves with marked RS-T segment depression in the precordial leads. The patient improved slightly in the next sixteen hours. The third electrocardiogram (Fig. 7,*C*) taken at that time showed a return to normal sinus rhythm with some improvement of the RS-T segment and T-wave deviations in most of the standard and chest leads. The T waves in Leads III and CR_2, however, had become more abnormal than in the previous record.

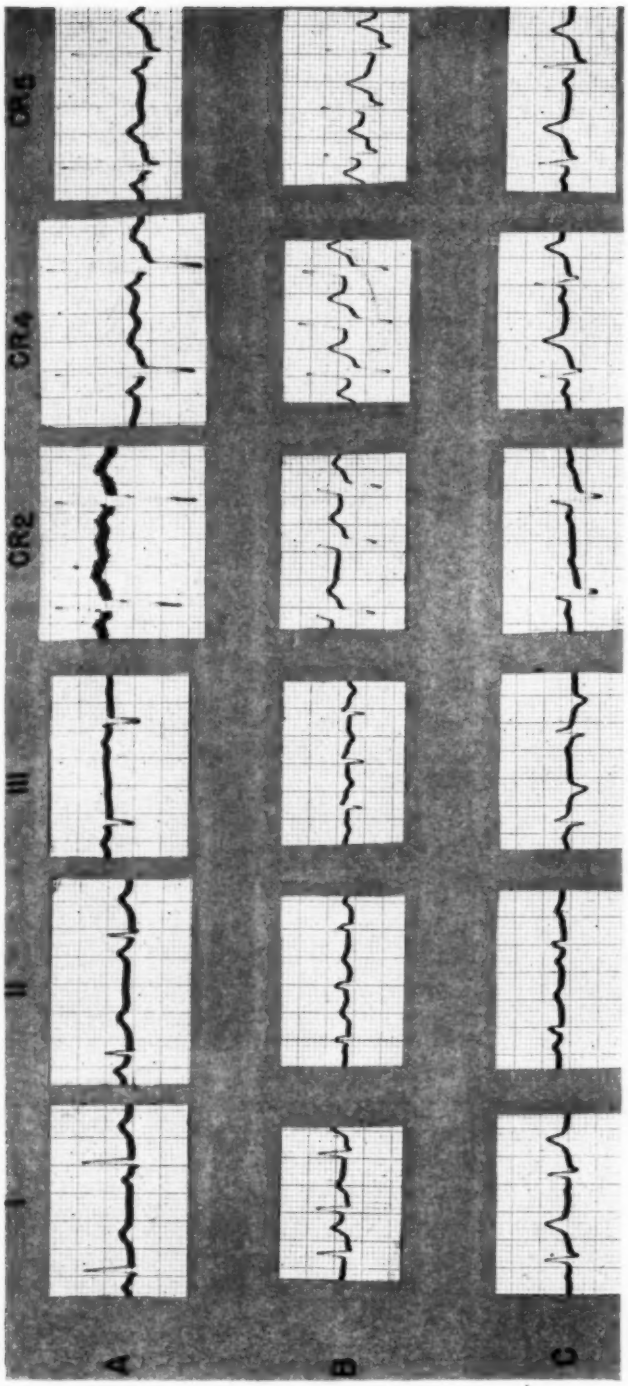

Fig. 7.—Electrocardiograms of patient F. W., a 62-year-old woman with carcinoma of the uterus with metastases. She developed pulmonary embolism with shock and collapse on Dec. 3, 1948. Record *A* was taken on Nov. 11, 1948, before the onset of the attack of pulmonary embolism. Record *B* was taken three hours after the attack and record *C* the following morning. For a discussion of the electrocardiographic findings see Case 7.

A STUDY OF THE ELECTROCARDIOGRAPHIC FINDINGS

In addition to the standard leads, multiple precordial leads of the central terminal of Wilson[9,11] and the augmented "unipolar" extremity leads of Goldberger[8] were employed in the study of four of the seven cases of pulmonary embolism in this series. The study yielded interesting information in Cases 1, 2, and 3, where minor pulmonary emboli were suspected clinically (Figs. 1, 2, and 3). The electrocardiogram was obtained within two hours of the acute pulmonary episode in each of these patients. A common electrocardiographic pattern consists of: (1) a sinus tachycardia, (2) prominent Q and inverted T waves in Lead III, (3) a prominent S wave in Lead aV_L, but with little or no S wave in Lead I, (4) a generalized lowering of all waves in all leads, especially marked in the leads that record the potentials of the epicardial surface of the left ventricle, and (5) some shift of the transitional region to the left. This pattern appeared almost immediately following the pulmonary embolism and often returned to nearly normal in a few hours time. A mild degree of tachycardia and a lowering of the amplitude of all waves may persist for a few days.

The electrocardiograms of Case 4, obtained seventeen and forty-eight hours, respectively, after a massive pulmonary embolism (Fig. 4,*A* and *B*), present a number of changes which are suggestive of both the pattern of acute cor pulmonale and the axis shift of minor pulmonary embolism. The electrocardiograms of Cases 5 and 6 (Figs. 5 and 6) are quite characteristic of the acute cor pulmonale pattern of McGinn and White[1] and Durant.[5] Clinically, both of these patients were in severe respiratory distress with signs of shock. There was, however, no inversion of T waves in the precordial leads noted in either of them during the acute phase of the disease. A second electrocardiogram of Case 5, made on the second day following pulmonary embolism (Fig. 5,*B*), showed lowering and inversion of the RS-T segments and T waves, respectively, from V_1 and V_3 positions. The RS-T segment and T-wave depressions seen in Fig. 6,*B* and *C* were probably mainly due to digitalis therapy. This patient also had arteriosclerotic heart disease and developed auricular fibrillation with the onset of the pulmonary embolism.

The electrocardiogram of Case 7 (Fig. 7), who was in severe and prolonged shock after massive pulmonary embolism, showed a multitude of electrocardiographic abnormalities. The records show a transient auricular fibrillation with rapid ventricular rate, a few characteristics of the acute cor pulmonale pattern, a mild degree of intraventricular conduction delay of right bundle branch block type, T waves of low amplitude in Lead CR_2, RS-T segment depression in all the chest leads, and a markedly decreased amplitude of all waves in all leads (Fig. 7,*B* and *C*). By comparing the precordial electrocardiograms of Fig. 7,*B* and *C*, it appears that some shift of the transitional area to the left had also occurred following the pulmonary episode.

DISCUSSION

By using aV extremity and multiple chest leads (V leads), a fairly consistent group of electrocardiographic abnormalities have been recorded, which may be of help in the diagnosis of minor pulmonary embolism. The findings observed

can be explained by the altered physiology of circulation due to pulmonary embolism.

A number of clinical and experimental studies have shown that, even with a small embolism, there is a marked elevation of pressure in the pulmonary artery and the right ventricle with dilatation of the right cardiac chambers and a decrease in cardiac output.[1,3,12-19,30] The dilated right ventricle then bulges and projects itself in the anterior plane of the body in the precordial region. In such a position, the electrical potentials of the left arm may develop an S wave. Hence, an RS type of QRS complex with varying depth of S waves is inscribed in Lead aV_L. Similar changes have been observed in Lead I (S_1 waves), but the S waves are present only in relatively small numbers of patients with pulmonary embolism. This is because of the negativity of the normal right arm potential, which goes into the making of Lead I. The lowering of the T waves in Lead aV_L, often seen with the QRS changes, may be related to some right ventricular ischemia secondary to the great increase in intraventricular pressure and diminished coronary blood flow.

When the right ventricle dilates, the heart is rotated on its anteroposterior axis and assumes a relatively vertical position in the chest. The shift to a vertical position is usually accompanied by mild degrees of clockwise rotation on the longitudinal axis and some posterolateral displacement of the left ventricle.[20,22,31]

The reduction of voltage of all positive waves in the limb and precordial leads probably represents a diffuse functional disturbance of the myocardium due to decreased cardiac output and venous drainage of the heart, which result in a marked lowering of the coronary blood flow.[12-19,29]

Since Lead III records the difference between the left leg and left arm electrical potentials, an initial downward deflection, Q wave, will be produced whenever the left leg potential is comparatively less positive or more negative than the left arm potential.[21] The conditions which favor the production of a Q wave in Lead III in cases of pulmonary embolism are: (1) When the heart assumes a relatively vertical position in the chest, the left shoulder (left arm) will tend to record the cardiac potentials of the right side of the interventricular septum, and the left leg will record the potentials of the left. At the instant when the depolarization is going through the interventricular septum, the right side of the septum (left arm) is more positive than the left side (left leg). (2) Disturbances of the arterial and venous circulations of the myocardium will tend to lower the voltage of the positive waves, for example, the R wave in the QRS complex. Since the main QRS deflection in the left leg lead is a tall R wave when the heart is vertically placed, a marked reduction of the voltage of the positive wave may make the electrical potentials of the left leg less positive than that of the left arm. The development of a Q wave in Lead III thus depends upon the degree of shifting of the electrical axis of the heart and of the circulatory disturbance of the myocardium produced by the pulmonary embolism.

The inversion of T waves and/or depression of the RS-T segments in the precordial leads have been reported by many observers.[1,2,11,23,24,28] These electrocardiographic abnormalities were observed in Cases 5, 6, and 7. These patients presented alarming symptoms of cardiorespiratory embarrassment and shock.

In Cases 1, 2, and 3, however, with minor clinical manifestations of pulmonary embolism, there were no significant RS-T segment and T-wave changes suggestive of decreased coronary blood flow or myocardial damage[3,6,7,12,25,26,28] noted in the precordial leads.

It is of some interest to note that two of this series of seven cases developed auricular fibrillation soon after the onset of pulmonary embolism, but normal sinus rhythm was resumed in both a few hours later. This observation is in accord with the experience of other investigators in clinical and experimental cases of pulmonary embolism.[12,19,27]

SUMMARY

1. A series of seven proved cases of pulmonary embolism with acute cor pulmonale presenting various electrocardiographic abnormalities has been studied.

a. Three patients with minor clinical episodes of pulmonary embolism showed a transient shift of the electrical axis of the heart to a relatively vertical position and a slight to moderate degree of clockwise rotation on its long axis with slight posterior displacement of the apex. This electrocardiographic pattern has been discussed in the light of the present knowledge of the physiology of the circulatory system in experimental pulmonary embolism.

b. The electrocardiogram of one of the patients taken eighteen hours after an attack of massive pulmonary embolism showed a few of the findings characteristic of both the classical acute cor pulmonale pattern and a shift of the electrical axis seen in cases of minor episodes of the pulmonary insult.

c. The electrocardiograms of the three remaining patients were quite characteristic of the acute cor pulmonale pattern with minor intraventricular conduction delay of the right bundle branch block type and marked RS-T segment and T-wave deviations suggestive of coronary insufficiency.

d. Prominent Q waves were observed in all seven patients in this series following the attack of acute pulmonary embolism.

2. The electrocardiogram may offer considerable help in the diagnosis of acute cor pulmonale. The record should be taken as soon as possible after the acute attack. The use of augmented unipolar limb and multiple central terminal chest leads is advocated. By means of this study, one may observe prominent S waves in Lead aV_F and a shift of the electrical axis in the absence of suggestive changes in the conventional leads.

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ADDENDUM

Since this paper has been prepared for publication, Phillips and Levine (Phillips, E., and Levine, H. D.: A Critical Evaluation of Extremity and Precordial Electrocardiography in Acute Cor Pulmonale, AM. HEART J. **39**:205, 1950) have reported their experiences with the use of unipolar leads in seven proved cases of acute cor pulmonale. They are also of the opinion that the unipolar limb and precordial leads, especially the latter, are frequently a valuable adjunct to the electrocardiographic diagnosis of acute cor pulmonale.

REFERENCES

1. McGinn, S., and White, P. D.: Acute Cor Pulmonale Resulting From Pulmonary Embolism; Its Clinical Recognition, J. A. M. A. **104**:1473, 1935.
2. Barnes, A. R.: Diagnostic Electrocardiographic Changes Observed Following Acute Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **11**:11, 1936.
3. Sokolow, M., Katz, L. N., and Muscovitz, A. N.: The Electrocardiograms in Pulmonary Embolism, Am. Heart J. **19**:166, 1940.
4. Love, W. S., Jr., and Brugler, G. W.: Electrocardiograms Similar to Those of Coronary Thrombosis With Especial Reference to Those Obtained in Pulmonary Infarction, South. M. J. **30**:371, 1937.
5. Durant, T. M., Ginsberg, I. W., and Roesler, H.: Transient Bundle Branch Block and Other Electrocardiographic Changes in Pulmonary Embolism, Am. Heart J. **17**:423, 1939.
6. Currens, J., and Barnes, A. R.: The Heart in Pulmonary Embolism, Arch. Int. Med. **71**:325, 1943.
7. Master, A., Dack, S., Grishman, A., Field, L., and Horn, H.: Acute Coronary Insufficiency: An Entity; Shock, Hemorrhage and Pulmonary Embolism as Factors in Its Production, J. Mt. Sinai Hosp. **14**:8, 1947.
8. Goldberger, E.: A Simple Electrocardiographic Method of Obtaining Augmented Unipolar Extremity Leads, Am. Heart J. **23**:483, 1942.
9. American Heart Association: Standardization of Precordial Leads, Am. Heart J. **15**:107, 235, 1938.
10. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, Am. Heart J. **9**:477, 1934.
11. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., de Oliveira, R., and Barker, P. S.: The Precordial Electrocardiogram, Am. Heart J. **27**:19, 1944.
12. Durant, T. M., Long, J., and Oppenheimer, M. J.: Pulmonary (Venous) Air Embolism, Am. Heart J. **33**:269, 1947.
13. Megibow, R. S., Katz, L. N., and Steintz, F. S.: Dymanic Changes in Experimental Pulmonary Embolism, Surgery **11**:19, 1942.
14. Buchbinder, W. C., and Katz, L. N.: The Electrocardiograms in Acute Experimental Distention of the Right Heart, Am. J. M. Sc. **187**:785, 1934.
15. Farr, C. E., and Spiegel, R.: Pulmonary Infarction and Embolism, Ann. Surg. **89**:481, 1929.
16. Hampton, H. H., and Wharton, L. R.: Venous Thrombosis and Pulmonary Infarction and Embolism Following Gynecological Operation, Bull. Johns Hopkins Hosp. **31**:95, 1920.
17. White, P. D., and Brenner, O.: Pathological and Clinical Aspects of the Pulmonary Circulation, New England J. Med. **209**:1261, 1933.
18. White, P. D.: The Acute Cor Pulmonale, Ann. Int. Med. **9**:115, 1935.
19. Love, W. S., Jr., Brugler, G. W., and Winslow, N.: Electrocardiographic Studies in Clinical and Experimental Pulmonary Embolism, Ann. Int. Med. **11**:2109, 1938.
20. Goldberger, E.: Unipolar Electrocardiography: Including Standard Leads, Unipolar Extremity Leads and Multiple Unipolar Precordial Leads, Philadelphia, 1947, Lea & Febiger.
21. Goldberger, E.: The Differentiation of Normal From Abnormal Q Waves, Am. Heart J. **30**:341, 1945.
22. Gardberg, M., and Ashman, R.: The QRS Complex of the Electrocardiograms, Arch. Int. Med. **72**:210, 1943.
23. Katz, L. N.: Electrocardiography; Including an Atlas of Electrocardiograms, ed. 2, Philadelphia, 1946, Lea & Febiger, p. 404.
24. Wood, P.: Pulmonary Embolism; Diagnosis by Chest Lead Electrocardiography, Brit. Heart J. **3**:21, 1941.
25. Currens, J.: The Electrocardiogram in Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **17**:502, 1942.
26. Visscher, M. B.: The Restriction of the Coronary Flow as a General Factor in Heart Failure, J. A. M. A. **113**:987, 1939.
27. Frommel, E.: Les troubles au rythme cardiaque au cours de l'embolie pulmonaire mortelle, etude electrocardiographique experimentale, J. de physiol. et de path. gém. **26**:247, 1928.
28. Flasher, J., Essex, H. E., and Barnes, A. R.: An Experimental Study of Acute Pulmonary Arterial Obstruction, With Special Reference to the Precordial Electrocardiogram, Am. Heart J. **36**:882, 1948.
29. Unghváry, L.: The Electrocardiographic Diagnosis of the Disturbances of the Heart's Venous Circulations, Am. Heart J. **37**:582, 1949.
30. Smith, J. R., and Hara, M.: Cardiovascular Dynamics in Experimental Embolism of Restricted Portions of the Lungs, J. Clin. Investigation **27**:556, 1948.
31. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram, Advances Int. Med. **2**:1, 1947.

THE RELATIONSHIP OF LEAD II TO LEAD I IN POSTERIOR INFARCTION AND ITS BEARING ON THE CONFIGURATION OF LEAD aV_F

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THE controversy on the relative merits of the standard limb leads and of the augmented Wilson limb leads in the diagnosis of posterior myocardial infarction was brought into sharp focus by the almost simultaneous appearance of two articles by competent observers with apparently contradictory conclusions. Lowen and Pardee[2] state that "The criteria derived from the unipolar limb leads are not dependable in the diagnosis of posterior infarction. The conventional limb leads more often give a positive sign." On the other hand, Myers and associates[1] state "Because of the demonstrated inferiority of the evidence furnished by the standard leads to that furnished by Lead aV_F for diagnosis of posterior infarction, a statistical summary of the findings in the standard leads in this series of 110 cases does not justify the space required." These two diametrically opposite conclusions may simply be an expression of the greater interest and experience that one group of observers has with one set of leads. The different conclusions may also be due to different criteria used by each group for the diagnosis of posterior infarction by the augmented Wilson leads. These latter leads are of comparatively recent origin, and new requirements for the criteria of both the normal and the abnormal are still being introduced. It has not been stressed in the recent contributions on these leads that there are but two independent equations that represent both the three conventional limb leads and the three Wilson limb leads. Any variation in one set of leads must lead to a variation in the other set of leads. One is a translation of the other. One set of leads may be more readily interpreted than another either because the language of one set of leads is more familiar to the interpreter or because of a general theory that is applicable to one set and not to the other. The purpose of this paper is to show that there is no intrinsic diagnostic superiority of one set of leads over the other for the diagnosis of posterior myocardial infarction.

Regardless of the theoretical significance of the augmented Wilson extremity leads, they are graphic registrations of mathematical derivations of the conventional standard limb leads. The derivation is most clearly seen by noting the relationship of Leads I and II to Lead III and to Lead aV_F.

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(1) Lead III = Lead II − Lead I.
(2) Lead aV_F = Lead II − ½ Lead I.

The proof for equation (1) is as follows:

Lead II = Lead III + Lead I.

This equation is correct because the potential difference between the right arm and the left leg is the same whether it is measured directly from the right arm to the left leg or through a circuitous path that passes through the left arm. Therefore, Lead III = Lead II − Lead I.

The proof for equation (2) is as follows:

$$aV_F = 3/2V_F = 3/2\left(F - \frac{R + L + F}{3}\right)$$
$$= 3/2\ (1/3\ [F\text{-}R] + 1/3\ [F\text{-}L]\ )$$
$$= 3/2\ (1/3\ L2 + 1/3\ L3)$$
$$= 3/2\ (1/3\ L2 + 1/3\ L2 - 1/3\ L1)$$
$$= L2 - 1/2\ L1.$$

These equations hold true of course only in an ideal situation in which the skin resistances are equalized and all artifacts have been eliminated.

Therefore, a Q wave will appear in Lead III if the initial potential of visible duration in Lead I is positive to the simultaneous initial potential of Lead II, but a Q wave will appear in Lead aV_F only if one-half of the initial potential of visible duration in Lead I is positive to the entire initial potential of visible duration in Lead II. It is for this reason that a Q wave may be present in Lead III and not in Lead aV_F. On the other hand, a Q wave may be present in Lead aV_F and absent in Lead III, because of the presence of a small Q wave in Lead I that when halved in amplitude either becomes of invisible duration or is cancelled by the R wave of Lead II. It, therefore, follows that a Q wave can appear in Lead aV_F only if the increase in voltage per unit of time of R_2 is considerably less than that of R_1. This delay in ascension of R_2 may make manifest a preceding negative wave from points in the myocardium distal to the positive electrode. This wave is called a Q wave and it represents, in the presence of infarction, a secondary manifestation of infarction. It represents the electrical impulse that is passing through the muscle that is not part of the infarcted muscle under study. The primary disturbance is in the R wave, the wave that represents the passage of the electric impulse through the infarcted muscle under study. This whole picture is exaggerated because infarction frequently reduces the total voltage through the infarcted region. This reduced voltage and decrease in voltage per unit of time is the sine qua non for the electrocardiographic diagnosis of infarction. The more obvious finding is the unmasking of a Q wave, so that this wave has been generally regarded as the pathognomonic sign of old infarction. The pathognomonic sign is focal myocardial block.

That the Q wave is not the primary manifestation of infarction is indicated by the fact that Myers does not hesitate to make a diagnosis of posterior infarction in the absence of Q_{AVF} provided that R_{AVF} is slurred or notched and slow in ascension. It is apparently not clearly recognized that R_{AVF} has these characteristics in posterior infarction with or without a Q_{AVF}. Furthermore, the

introduction of the "electrical position" of the heart in the interpretation of the significance of Q_{AVF} is another way of stating that the electrical potential of the left arm influences the Wilson left leg lead. It is obvious from equation (2) that the amplitude of Q_{AVF} will depend upon the amplitude of R_1 in addition to the time interval between the beginning of Q and the first visible positive potential at the left leg. These relationships are as clearly seen in Leads I and II as in Lead aV_F. A comparison of the duration of QR_2 and that of QR_1 and of the amplitude of R_1 and R_2 for the diagnosis of posterior infarction is not unlike the method used in the diagnosis of infarction by precordial leads. Because all portions of the myocardium are not activated simultaneously, there are differences in duration of the normal wave as different regions of muscle are tapped.

To determine the difference in duration between QR_2 and QR_1 that is significant for a diagnosis of posterior infarction, an analysis was made of the duration of QR and the amplitudes of the R waves in Lead I and in Lead II in thirty-five consecutive instances, that were diagnosed by the usual signs in the standard or Wilson limb leads as posterior infarction and later proved by necropsy (Table I).

From this table, it can be seen that the Q-R interval in each instance was greater in Lead II than in Lead I, even though the amplitude of R_2 was less than R_1 in twenty-nine of the thirty-five cases. In those instances in which R_2 was of lower amplitude than R_1, which is usually seen, the duration of QR_2 was at least 0.02 second longer than the duration of QR_1 to a point on R_1 that is equipotential with the summit of R_2. It is also to be observed that QR_2 was at least 0.06 second in duration, except when low amplitude was present. Even in low amplitude the duration of QR_2 was at least 0.04 second. In these instances of low voltage QR_2 was at least 0.01 second longer than that fraction of QR_1 which is isopotential with the summit of QR_2.

Our limited autopsy material suggests that in posterior infarction, if measured from the beginning of the QRS complex, at least 0.06 second is required for the R_2 wave to rise 10 mm. and, if the R_2 wave is as low as 5 mm., at least 0.04 second is required. On the other hand, in the normal, the R_2 wave may rise 10 mm. in as short a time as 0.02 second. This displacement of the R wave to the right can clearly be seen in those instances in which electrocardiograms are taken both before and after infarction. If the Q wave were the primary electrocardiographic change in infarction, then whatever portion of the subsequent R wave appears should appear on time. But in all instances, the R wave appeared late, relative to the R wave of the uninfarcted region (Lead I), to that found before infarction occurred, and to that usually seen in normal tracings. This delay is indicative of focal myocardial block.

Because of the limited number of necropsies, an analysis was made of R_2 and R_1 in the electrocardiograms of 1,000 consecutive individuals who were referred for electrocardiographic study. Of these 1,000, 766 had R_2 of greater amplitude than R_1. In this group only two posterior infarcts were found. In one instance R_2 was 0.02 second longer than R_1, and in the other 0.04 second longer. Two hundred and thirty-four had R_1 of greater amplitude than R_2.

TABLE I. THE DURATION OF QR AND THE AMPLITUDE OF R IN LEAD I AND IN LEAD II IN 35 CONSECUTIVE INSTANCES OF POSTERIOR INFARCTION PROVED BY NECROPSY

CASE	DURATION		AMPLITUDE	
	QR_1	QR_2	R_1	R_2
1	0.05	0.06	19	8
2	0.06	0.08	6	7
3	0.04	0.08	5	1
4	0.03	0.06	2	2
5	0.04	0.06	16	2
6	0.08	0.08	12	6.5
7	0.06	0.08	6	5
8	0.06	0.08	6	5
9	0.06	0.08	5	0
10	0.06	0.08	19.5	7.5
11	0.04	0.06	12	9
12	0.04	0.06	3	1
13	0.05	0.08	4	2
14	0.06	0.08	7	5
15	0.06	0.08	6	4
16	0.06	0.08	6	8
17	0.04	0.08	12.5	5
18	0.04	0.08	8	9.5
19	0.04	0.06	11	5
20	0.07	0.08	11	4
21	0.03	0.07	13	8.5
22	0.03	0.04	4	5
23	0.04	0.06	5.5	3
24	0.06	0.09	9	2
25	0.04	0.06	8.5	6.5
26	0.04	0.07	6.5	11.5
27	0.03	0.06	8	6
28	0.03	0.06	8	5
29	0.04	0.06	7	6
30	0.06	0.08	5	3
31	0.04	0.06	3	0
32	0.02	0.04	5	5
33	0.03	0.10	3	7
34	0.04	0.08	15	6
35	0.06	0.08	16	8

Of these, 160 had R_1 of greater duration than R_2. No posterior infarct was present in the group. In 74, R_2 was greater in duration than R_1. Thirty of these had other electrocardiographic signs of infarction. Twelve had bundle branch block. Twelve had hypertension with R_2 of large voltage (18 to 22 mm.), but R_2 was shorter in duration than that fraction of R_1 taken at half sensitivity which was equipotential with R_2. Sixteen had no other electrocardiographic evidence for infarction, but all had pain on effort. Of these, six had severe hypertension, two had heart failure, two had other signs of myocardial disease such as negative precordial T waves, and six had no other detectable evidence of myocardial disease except for the pain on effort. Four had neither symptoms nor other signs of myocardial disease.

From this study, it appears that in healed posterior infarction that can be recognized by electrocardiography, R_2 takes 0.06 second to rise 10 mm. and in low voltage 0.04 second to rise 5 mm. In low voltage, it is at least 0.01 second

longer than the point on R_1 that is isopotential with the summit of R_2, and, when R_2 is 10 mm. or more, it is at least 0.02 second longer than the isopotential point on R_1. It is well known that high voltage is not commonly seen in the lead that taps the infarction. Therefore, an R wave greater than 15 mm. in Lead II is uncommonly seen in posterior infarction. But even in these instances, the duration of R_1 is shorter than that fraction of R_2 which is equipotential with the summit of R_1. Of course, these relationships may not hold for combined anterior and posterior infarction. On the other hand, neither may the Q waves be present in aV_F. If the Q wave in Lead I is more than twice the length and of shorter duration than the Q wave of Lead II, a Q wave cannot appear either in Lead III or in Lead aV_F. The diagnosis then first depends on demonstrating a duration of R_2 that is definitely outside the limits of normal.

Wilson, in his now classic papers,[3] was the first to indicate the mathematical relationship between the potential variations of the standard leads and that of a single extremity. His formulas, which assume the tenability of the Einthoven hypothesis, indicate that one is simply a translation of the other. Equation (2) is a simple relationship between the two which is independent of the Einthoven hypothesis. Wilson also clearly pointed out that, unlike the standard leads which faithfully record the differences in potential between two extremities, artifacts are introduced in the attempt to obtain the potential variation of a single extremity because of the unequal resistances between the three extremities and the central terminal. He thought that the artifact could be reduced to clinical insignificance by interposing sufficient resistance between each extremity and the central terminal. Although all this is clearly stated by him, many workers in electrocardiography used central terminals that did not correct for these artifacts. It became necessary, after many years, for Bryant and Johnston[4] and Rappaport and Williams[5] to re-emphasize the magnitude of the artifacts introduced into the extremity electrocardiogram by the absence of or insufficient resistance.

Similarly, there has been a recent attempt to prove that the standard leads are intrinsically superior or inferior diagnostically to the Wilson leads, even though one is a direct mathematical derivation of the other.

All comparative studies of the value of the standard limb leads and the augmented Wilson leads for the diagnosis of posterior infarction are based upon a comparison of the values of Q_2, Q_3, and Q_{AVF}. These three waves do not represent electrical events in similar anatomic portions of the myocardium, nor indeed does any one of them represent any electric phenomenon passing through the infarcted muscle. Any portion of the curve in one type of lead is correctly compared only to the homologous portion of the curve in the other type of leads. The homologous portions in the standard leads for Q_{AVF} are portions of QR_2 and QR_1 and not Q_2 and Q_3. Indeed, it would appear that the standard leads, if taken simultaneously and accurately summated graphically, could be used as a test for the presence of artifacts introduced into the Wilson leads or any of their modifications.

Although one set of leads can be translated mathematically or graphically into the other, it does not follow that one set of leads may not be more readily

correctly interpreted than the other. The most important factor is the experience of the interpreter with each type of lead. The extremity leads of Wilson have the advantage that they are more easily interpreted in the light of a general theory of electrocardiography which has abundant experimental and pathologic evidence to support it, whereas the standard leads have to be interpreted either empirically or in the light of the general theory only after mathematical translations are made. It is important to remember that the Wilson extremity leads do not tap the same anatomic portion of the myocardium, or the same proportion of the entire myocardium from patient to patient, or even in the same patient from time to time, because of the variable distances of the heart from the extremities and the variable relationships of any specific portion of the myocardium to the bony skeleton. It is for these reasons that it was necessary to determine, by the same type of statistical analysis as was used for the standard leads, the normal variations of the Wilson extremity leads. Once these normals are clearly defined, it is much easier for the physician to visualize the nature of the electrical events as depicted in the Wilson leads than in the standard leads, provided that clinically significant artifacts are not introduced and provided that the Einthoven hypothesis is tenable.

CONCLUSIONS

1. The Wilson extremity leads are a translation of the standard leads.
2. There is no intrinsic diagnostic superiority of one over the other.
3. The Wilson leads, however, permit an easier visualization of the electrical events which occur during the heart cycle.

REFERENCES

1. Myers, G. B., Klein, H. A., and Hiratz, T.: Correlation of the Electrocardiographic and Pathologic Findings in Posterior Infarction, AM. HEART J. **38**:547, 1949.
2. Lowen, H. J., and Pardee, H. E. B.: Unipolar Extremity Leads in Records With Large Q_3, Ann. Int. Med. **31**:456, 1949.

3a. Wilson, F. N., Macleod, A. G., and Barker, D. C.: The Potential Variation Produced by the Heart at the Apices of Einthoven's Triangle, AM. HEART J. **7**:207, 1931.

3b. Wilson, F. N., Macleod, A. G., and Barker, P. S.: Electrocardiographic Leads Which Record the Potential Variations Produced by the Heart at a Single Point, Proc. Soc. Exper. Biol. & Med. **29**:1011, 1932.

3c. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, AM. HEART J. **9**:447, 1934.

4. Bryant, J. M., and Johnston, F. D.: Errors Encountered in the Use of the Goldberger Central Terminal, J. Clin. Investigation **25**:919, 1946.
5. Rappaport, M. B., and Williams, C. (with the editorial assistance of White, P. D.): An Analysis of the Relative Accuracy of the Wilson and Goldberger Methods for Registering Unipolar and Augmented Unipolar Leads, AM. HEART J. **37**:892, 1949.

THE ELECTROCARDIOGRAPHIC PATTERNS AND THE LOCALIZATION OF INTRAVENTRICULAR CONDUCTION DEFECTS

A Survey of the Method of Approach and Tentative Conclusions

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IN THE course of a study of the statistical value of multiple leads for routine clinical electrocardiography,[1] certain QRS contours were encountered which were believed to be evidence of defective intraventricular conduction but which could not be readily explained on the basis of a bundle branch block (BBB). The difficulty in localizing electrocardiographically the anatomic site responsible for the abnormality prompted us to study this subject in greater detail. As a basis for this study, the extensive literature concerned with the various types of defective intraventricular (IV) conduction was reviewed in a separate communication.[2] It was evident from this analysis that the question of the localization of a pattern of abnormal IV conduction to the right or left bundle branch system has mainly been resolved. The problem that remains is the differentiation of patterns indicative of defective impulse spread in the free walls of the ventricles from those due to abnormal transmission through the main bundle branches.

One hundred electrocardiograms in which the contour of the ventricular complexes and the duration of the QRS suggested defective IV conduction were selected from the recent files of the Heart Station. With a few exceptions, each record included the standard and aV limb leads and precordial leads V_1 to V_6 and V_{4R}. BBB complicated by confluent myocardial infarction was excluded. However, for purposes of developing the mechanisms of defective IV conduction, two cases of confluent myocardial infarction were included. During a preliminary examination the electrocardiograms were first divided into two groups to localize the conduction defect to the right or left bundle branch system; they were then subdivided with respect to the presence or absence of a known pattern of BBB.[3,4] Critical study of the collected records and careful analysis of previous investigations[2] led to certain tentative conclusions. These, together with the evidence upon which they are based, form the substance of this report. Since this is not a statistical analysis, no attempt was made to tabulate the incidence of the various types of IV conduction defects which were studied.

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BUNDLE BRANCH BLOCK

The studies of Lewis and Rothschild,[5] supported by Wilson and co-workers[4,6] among others, promulgated the classical concept of impulse transmission in the mammalian ventricle, based on the belief that specialized conduction tissue distal to the main bundle branches was essentially limited to the subendocardial Purkinje network; the sinus impulse was believed to travel rapidly through this plexus and then more slowly through the ordinary ventricular muscle in a direction more or less perpendicular to the endocardium. When the sinus impulse was prevented from passing normally down one or the other main bundle branch, the activation of the involved ventricle was believed to be due to a transeptal conduction from the contralateral normal side below the site of the block. Moreover, this was believed to occur through ordinary septal muscle, resulting in a slower spread of the impulse to the involved side,[7] the latter contributing materially to the prolongation of the QRS interval.[8] On the other hand, Abramson and Jochim[9] and others[2] have demonstrated the existence of an extensive intramyocardial network of specific conduction tissue in most of the free wall of the ventricles and in the septum; these peripheral ramifications are continuous with the subendocardial plexus and terminate directly in the ordinary muscle fibers. It is possible, then, that the transeptal spread below the site of a BBB may occur rapidly via specific conduction tissue and contribute little to the prolonged QRS duration.[10] Despite evidence to the contrary,[9] it is widely held that impulse conduction is much more rapid in the subendocardial plexus,[11] although the differential rates calculated by Lewis[5] may be somewhat in error. Simultaneous precordial and intraventricular cavity leads in dogs and in humans with BBB have confirmed the transeptal activation of the involved ventricle from the contralateral normal side.[12] Study of the published material suggests that this transeptal conduction may occur rapidly and display no evidence of an irregular course. In other instances it apparently proceeds at a somewhat slower rate and produces slurring; however, the role of hypertrophy or fibrosis in the septum has not been evaluated in this regard.

The localization of a BBB to the left or right ventricle can usually be made by comparing the pattern and particularly the time of onset of the "intrinsicoid" deflection in Leads V_1 and V_5. Occasionally, a marked shift of the transition zone to the right or left precordium may necessitate the presence of Lead V_{1R} or V_7 for accurate localization. The derivation of the pattern of right and left BBB has been clarified with the aid of intracavity leads in humans and in dogs.[4,12]

In right BBB, right-sided precordial leads usually display an rsR′ pattern in which the initial small R wave is ascribed[12] to the normal early left-to-right transeptal impulse spread below the site of block; the upper part of the upstroke of R′ and its downstroke would then be inscribed during the activation of the free wall of the right ventricle. These three phases are typically shown in Lead V_1 in Fig. 1, *A* and *D*. Left-sided precordial leads usually display an early slender R wave and a prominent broad S wave (Lead V_6, Fig. 1, *A*). Intervening precordial leads display complexes intermediate in form between those to their right or left. Fig. 1, *A*, *D*, and *F*, show patterns of right BBB in the horizontal "electrical" position commonly observed in such cases.

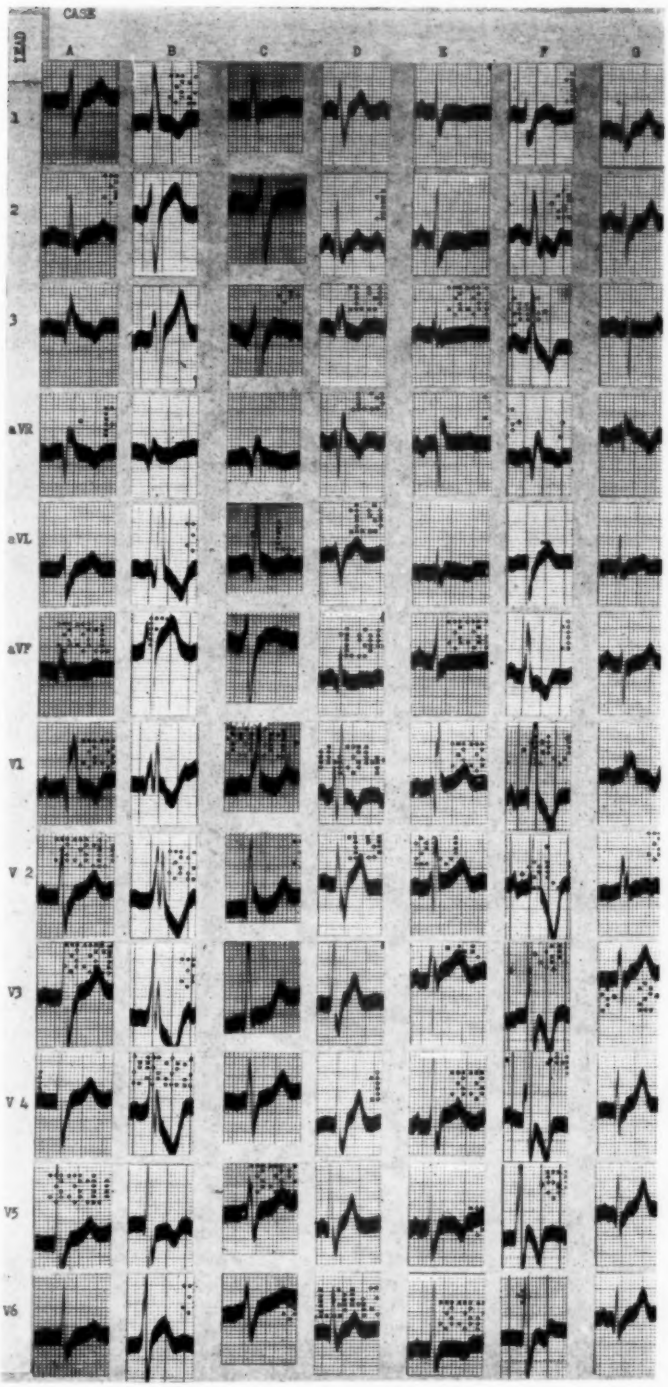

Fig. 1.—Seven instances of right-sided IV block. *A*, *B*, *C*, *D*, *G*, and *H* are cases of hypertensive and arteriosclerotic heart disease, which in Case *H* was associated with marked enlargement of the left ventricle. Case *E* had syphilitic heart disease with marked enlargement of the left ventricle and an aortic aneurysm. Case *F* had rheumatic heart disease, mitral stenosis, marked enlargement of the right ventricle and of the pulmonary artery. Discussed in text.

In a pattern of uncomplicated left BBB, left-sided precordial leads display an upright M-shaped ventricular complex consisting of a bifid R wave due to a large apical notch; this pattern is seen in Leads aV_L and V_5 in Fig. 2, *A*, an instance of left BBB in a horizontal "electrical" position. In other cases, these leads display an upright broad deflection which is slurred or flat-topped with a plateau at the apex (Lead V_6, Fig. 2, *B* and *C* and Lead V_5, Fig. 5). A Q wave is rarely present in these leads in either complete or incomplete left BBB in the absence of myocardial infarction.[4,13] Right-sided precordial leads consist of mainly inverted, widened deflections, frequently preceded by initial small R waves (Lead V_1, Fig. 2, *A*); intervening leads again are transitional in form.

The large amplitudes of the QRS and T waves have been explained[8] by the theory that unopposed forces developed during the activation and repolarization of each ventricle; the T wave is usually opposite in direction to that of the broadened QRS deflection. The pattern in Leads aV_L and aV_F may resemble either right-sided or left-sided precordial leads, depending on the "electrical" position. The standard limb lead patterns accordingly may vary widely.[14,15] It is for this reason that accurate localization of a BBB to the right or left ventricle must rest on the precordial lead pattern. This is shown in Fig. 2, *B*, which illustrates a pattern of left BBB in an unusual semivertical position and in Fig. 1, *B* and *C*, two instances of right BBB in a vertical position associated with a left axis shift in the standard limb leads. Although localization to the right ventricle may be suggested by the triphasic QRS complex in Lead I in Case *C* of Fig. 1,[4] such an interpretation based on the limb lead pattern is difficult in Case *B*. In right BBB the aV limb lead resembling left-sided precordial leads will frequently have an R wave smaller than its precordial analogue (Lead aV_L, Fig. 1, *A*, *D*, and *F*) or relatively smaller compared to the following S wave (Lead aV_F, Fig. 1, *C*).

In accordance with the concept of the derivation of the pattern of uncomplicated right BBB as elaborated for direct epicardial and intracavity leads,[4,12] theoretically, smooth, small initial rs waves would be expected in Lead V_1; it would further be anticipated that the upstroke of the final R′ deflection, supposedly inscribed by transeptal impulse spread below the site of block, might be slurred and prolonged and that the upper part of the upstroke and the downstroke of the R′ would be smoothly inscribed, since they supposedly represent the spread of the impulse through the subendocardial region and the free wall of the right ventricle. By analogy, in a pattern of left BBB, it would be anticipated, theoretically, that the initial portion of the bifid R wave, supposedly representing right-to-left transeptal conduction, might be slurred and that the final portion would be smoothly inscribed. These contours were rarely encountered in the present study.

Right BBB is best recognized in Lead V_1. However, the pattern often differs from the contours anticipated on the above theoretical grounds. On occasion, only an R wave, notched and slurred on its upstroke, is observed (Fig. 1, *C*). In some instances there is an absence of any slurring in Lead V_1 (Fig. 1, *D*). Thus, it would appear that in some cases, conduction across the IV system apparently seems to contribute little to the QRS interval prolongation.[10] Occasionally, the initial R wave is markedly slurred (Fig. 1, *B*), and in some in-

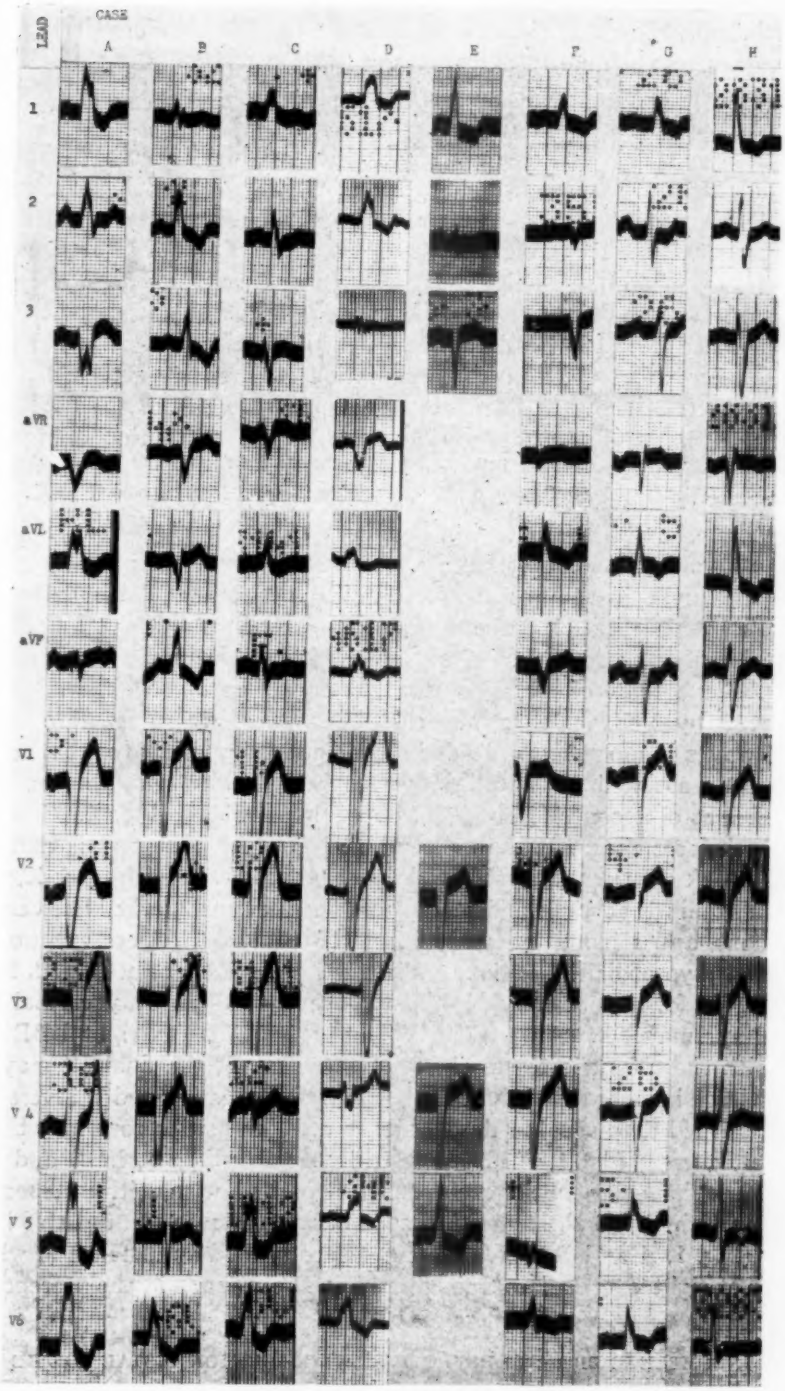

Fig. 2.—Eight instances of left-sided IV block. *A*, *B*, *C*, *D*, and *H* are cases of hypertensive and arteriosclerotic heart disease. Case *G* had chronic glomerulonephritis and was in renal failure. Records *E* and *F* were obtained within an interval of three months on a patient with old calcified endocarditis of the mitral and aortic valve. Discussed in text.

stances the upper part of the upstroke of the final R′ is slurred (Fig. 1, *A*). Not infrequently, the final R′ will be slurred throughout (Fig. 1, *G*). It is conceivable that myocardial fibrosis in the septum and/or free wall of either ventricle may be partly responsible for these variations.

An analogous situation was encountered in left-sided precordial leads in the cases of left BBB. The smooth contour of the upstroke and downstroke of the R wave in V_5 and V_6 in Figs. 2, *A* and 4, *G* was observed less often than was marked slurring (Lead V_6, Fig. 2, *B* and *C*), and, on occasion, a triphasic low R wave (Leads V_5 and V_6, Fig. 2, *D*) was seen. The smaller voltages usually observed with marked slurring and notching in leads over the right (in right BBB) and left side (in left BBB) (Lead V_1, Fig. 1, *G* and Lead V_6, Fig. 2, *B*, *C*, and *D*) can be explained on the assumption of extensive myocardial fibrosis in the free wall of the ventricles. Slurring may result from the devious path taken by the impulse in the presence of multiple patchy areas of myocardial fibrosis, and low voltage may likewise be caused by this aberrant course. This would appear to be consistent with views expressed previously[7,8,23,24,25] and with a recent study in this laboratory,[16] in which progressive increase in slurring and decrease in voltage were correlated with necropsy findings of diffuse, patchy myocardial fibrosis in the absence of confluent infarction. When a pattern of BBB was observed in such patients, the voltage was small and marked slurring was occasionally present.

We believe that, on occasion, the electrocardiographic diagnosis of BBB complicated by ventricular strain can be made. In a pattern of right BBB, T waves in most, or all, leads in a direction opposite to that expected and, when associated with tall R waves in left-sided chest leads, may be manifestations of a concomitant left ventricular strain.[17] Fig. 1, *E* is one of several such cases encountered in our study. The S-T-T pattern is that seen in patterns of left ventricular strain. The record was obtained from a 40-year-old man with syphilitic aortic insufficiency, aortic aneurysms, marked left ventricular enlargement, and a blood pressure of 210/150 mm. Hg. There was no clinical evidence of myocardial infarction. When left BBB is associated with left ventricular strain (or hypertrophy), in the absence of significant myocardial fibrosis, large voltage may be present (Lead V_5, Fig. 4, *G*). When right BBB is associated with right ventricular strain (or hypertrophy), the final R′ may be excessively large in right-sided chest leads, the S-T depression and T inversion may be more marked than usual in these leads, and the transition zone may be shifted to the left chest. Fig. 1, *F* illustrates this pattern of right BBB and marked right ventricular enlargement occurring in a patient with mitral stenosis. Ordinarily in right BBB the transition zone occurs towards the right of its usual position (Fig. 1, *A* and *D*). We have not encountered an instance in which the diagnosis of right ventricular strain could have been made in the presence of left BBB.

INCOMPLETE BBB AND DEFECTIVE IV CONDUCTION DISTAL TO THE MAIN BUNDLE BRANCHES (PERIPHERAL IV BLOCK)

It has been widely held that a beat of supraventricular origin having a QRS of 0.12 second or more indicates a complete BBB and one of 0.10 to 0.12

second an incomplete BBB in which the impulse is merely delayed in its passage down the main bundle branch.[18,19] Wilson and his associates believe that slurred, low-voltage QRS complexes widened to 0.12 second or more result from combined defective conduction in the bundle branches and in the free wall of the ventricles. More recently it has been realized that complete right BBB may be present with a QRS interval of only 0.10 second[4,19] and incomplete right BBB with a duration of little more than 0.08 second.[17] The differentiation of high-grade incomplete from complete right BBB may thus be difficult. It has further been realized that defective IV conduction distal to the main bundle branches might alone produce a widened QRS interval,[20] but the electrocardiographic diagnosis of peripheral IV block is rarely made.

The concept of peripheral IV block was introduced in 1916 under the term "arborization block"[21] and was ascribed to defective conduction in the subendocardial regions, produced by extensive fibrosis which involved the conduction tissue as well as ordinary muscle. This concept was largely discarded because of the absence of confirmation from experimental studies.[8,22] However, precordial leads were not employed in these studies, and they dealt largely with subendocardial lesions. It is apparent that scattered myocardial fibrosis might involve the conduction system located in various parts of the free wall[9,2] and interfere with normal impulse transmission in various regions of the ventricular walls. Thus, experimental trauma to the deeper layers of the myocardium has materially altered the course of the excitatory impulse across the free ventricular wall, although not changing the rate at which the impulse was propagated.[23] Clinically, abnormal patterns due to such changes would suggest defective left IV conduction since myocardial fibrosis consequent to chronic coronary artery insufficiency involves the right ventricle less commonly and to a lesser extent. Furthermore, abnormalities of peripheral right IV conduction might fail to be mirrored in the electrocardiogram because of the apparent domination by forces incident to activation of the left ventricle. Defective conduction consequent to fibrosis in the free wall of the left ventricle would elicit momentary changes in the direction of the spreading impulse[24,25] and produce momentary changes in the rate of impulse propagation. The resulting irregularity in the growth and decline of manifest potential differences, accentuated by simultaneous rapid and frequent changes in the direction of the mean electrical axis, would further tend to produce notching and slurring of the ventricular complexes.[8] Thus, slurring and low voltage would be expected under such circumstances and have actually been reproduced experimentally.[23] Significant slurring and notching of QRS in most leads are rarely seen in the absence of myocardial damage.[25,26]

In accordance with the principles by which the various deflections of precordial leads are interpreted,[27] such slurring might be anticipated in the initial portions of the upstroke of R in precordial leads over the left ventricle if the peripheral conduction defect occurred in the subendocardial region; it would be expected on the downstroke if the myocardial changes were limited to the subepicardial regions; slurring would be anticipated on both upstroke and downstroke if the lesions involved the entire left ventricular wall. If the entire

ventricle was involved, similarly altered QRS complexes would be expected in all leads, whereas, in the presence of a focal peripheral IV lesion, only leads recorded in its close proximity would be expected to reveal such changes. Patterns representative of such variously localized peripheral conduction defects have been recognized and designated by new terminologies,[20,35,36] the pattern in different leads varying according to the orientation of the exploring electrode. Significant widening of the QRS interval would be expected to occur only if the involved region were activated later than those parts of the heart normally activated last. The onset time of the "intrinsicoid" deflection would be expected to vary, depending on the localization of the lead with respect to the area of myocardium specifically involved.

Electrocardiographic patterns assumed to mirror such changes are commonly encountered in electrocardiographic practice and can be rationally interpreted by assuming various types of peripheral IV conduction abnormalities. The presence of the patterns, illustrated later, has been correlated clinically with cardiomegaly and chronic myocardial lesions.[28,29] Furthermore, one would expect that serial electrocardiograms recorded over a period of years in patients with progressive patchy myocardial fibrosis incident to chronic coronary insufficiency would reveal such changes even in the absence of confluent myocardial infarction. These findings were substantiated in this department.[16] Serial tracings in ninety-five patients found at necropsy to have moderate to extensive patchy myocardial fibrosis without confluent infarction often demonstrated progressively decreased voltages, progressively increased slurring, and, occasionally, widening of the QRS interval. When the pattern of BBB was observed in such cases, there were often associated small voltages and/or marked slurring, suggesting the possibility of superimposed defective peripheral IV conduction.

The electrocardiographic pattern of moderate to advanced ventricular strain (hypertrophy) has also been explained in part by assuming a peripheral delay in impulse transmission, variously ascribed to a mechanical lengthening of the subendocardial Purkinje system associated with cardiac enlargement, to fibrosis in the subendocardial region, to a thickened ventricular wall, and to subendocardial ischemia.[22,30] The QRS interval is often variously increased with patterns of ventricular strain.[28] Fig. 2, *E* shows a pattern of left ventricular strain, widening of the QRS interval to 0.10 second, and slurring of the upstroke of the R waves in Leads I and V_5, which suggests the possibility of a delay in impulse propagation mainly in the subendocardial layer of the left ventricle. In other records of this type, a Q wave in left-sided precordial leads may help to rule out a concomitant incomplete left BBB,[4,13] particularly when the bifid R-wave pattern is not present in these left-sided precordial leads. When this bifid R-wave pattern is present in a pattern of left ventricular strain, the differentiation of incomplete left BBB from a peripheral delay in conduction may be impossible at present. Fig. 3, *A* illustrates a similar situation in a pattern of right ventricular strain. The late onset time of the "intrinsicoid" deflection in Lead V_1 indicates a delayed right ventricular activation. The QRS interval is 0.12 second, and the differentiation from concomitant delay in the right bundle branch cannot be made. In other cases of right ventricular strain when the

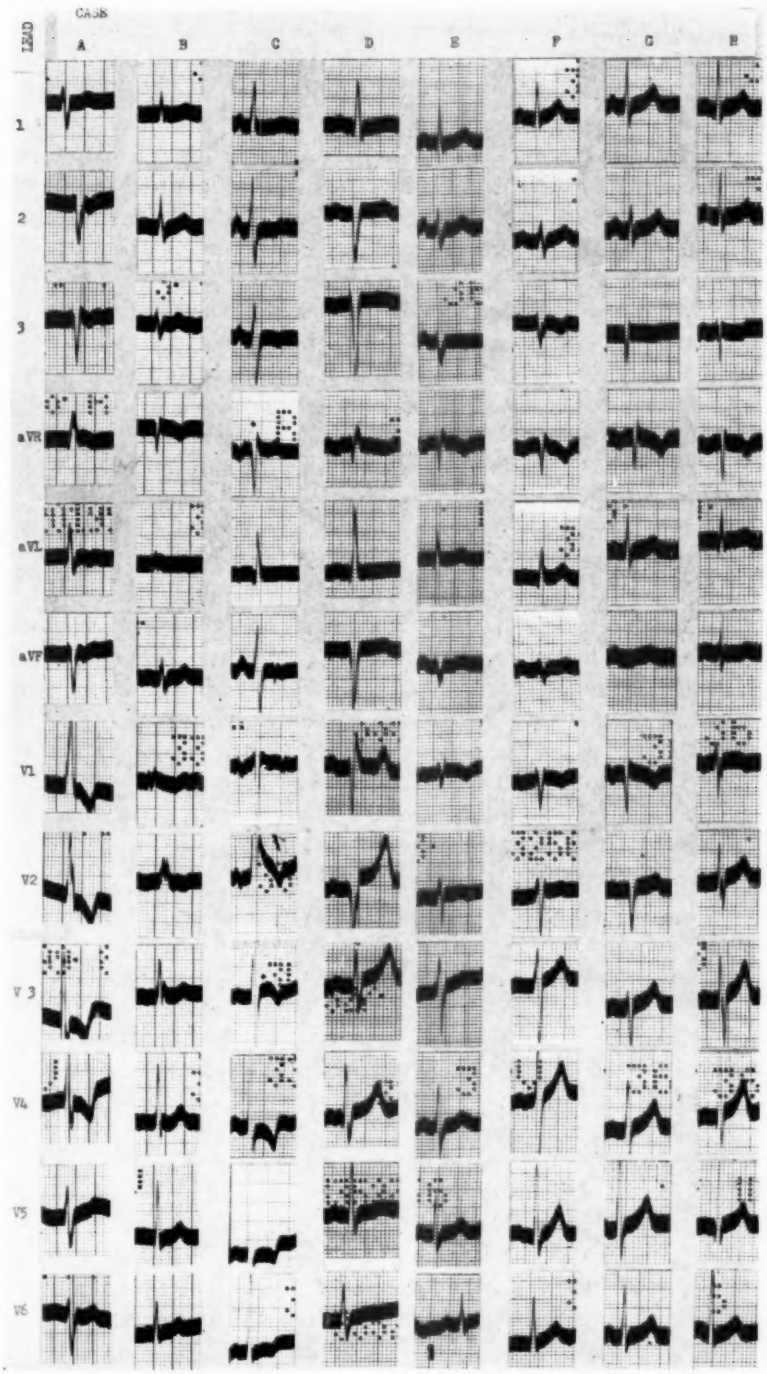

Fig. 3.—Different patterns representing abnormal (*A* to *E*) and normal (*F* to *H*) conduction delay within the ventricles. Cases *A* to *E* had arteriosclerotic heart disease; Case *G* had hypertension; Cases *F* and *G* had no clinical evidence of heart disease. Discussed in text.

QRS interval is widened less and when there is only an R wave in V_1, slurred on its upstroke, the assumed element of delayed subendocardial impulse propagation may be present, similar to cases of left heart strain (Fig. 2, *E*). It is possible that such cases reflect a delay in passage of the impulse down the main bundle branch as well as in the subendocardial areas of the free wall. On the other hand, when there is only slight widening and when the bifid R-wave pattern is absent, it may be that the subendocardial delay predominates in effecting the QRS prolongation and the slurred upstroke of the R wave. All of these matters demand further objective study.

Since the subendocardial region of the left ventricle is the first and most intensely affected in hypertensive and arteriosclerotic heart disease by ischemia and later fibrosis, a pattern such as in Fig. 2, *E*, in which slurring is limited to the upstroke of the R wave in left-sided precordial leads, would be expected to be encountered early in the course of the disease. When the myocardial ischemia and consequent patchy fibrosis later extend throughout the entire thickness of the ventricular wall, progressive changes can occur in serial tracings. Fig. 2, *F* was obtained from the same patient as record *E* and illustrates the typical progression; there is further widening of the QRS interval to 0.12 second, marked increase of slurring throughout QRS, and a noticeable decrease in voltage. Such records have recently been termed "anterior arborization block"[35] and "parietal block."[20] The presence of the small Q wave in Leads I and aV_L in the absence of a demonstrable myocardial infarction again tends to rule out left BBB.[4,13] Similar changes were found in serial records in patients with progressive myocardial fibrosis in the absence of left ventricular enlargement, except that the early pattern of left ventricular strain was not seen.[16] Thus, such changes can be ascribed to the presence of diffuse, patchy myocardial fibrosis leading to defective peripheral IV conduction across the free wall of the left ventricle in the manner already discussed.

It has recently been accepted by Wilson and associates[27] that the downstroke of the R waves in left-sided precordial leads is inscribed during the activation of the subepicardial regions of the left ventricle.[33,34] Thus, defective IV conduction in the outer layers of the left ventricle might be expected to produce an abnormal downstroke of the R waves in left-sided chest leads if the lesion were limited to the anterior wall of the left ventricle; because of the different orientation of the anterior chest electrodes to the posterobasal region, similar lesions in the posterior wall might lead to a late slurred S wave in these leads. Fig. 2, *G* illustrates the pattern expected in the former case. The QRS interval measures about 0.10 second. Although the bifid R-wave pattern closely resembles the pattern seen in incomplete left BBB, the presence of tiny Q waves in left-sided precordial leads, in the absence of demonstrable myocardial infarction, rules against such an interpretation.[4,13] Fig. 2, *H* illustrates the pattern assumed to be caused by regional conduction delay in the left posterior ventricular wall, involving the subepicardial region. The presence of slurred, broad S waves in left-sided chest leads would suggest a delay in conduction through the right ventricle, but the absence of late R′ waves in the right chest leads helps to differentiate these patterns. The notching on the upstroke of the S waves in

right-sided chest leads and the slurred R in aV_R, coincident with the late S wave in the left-sided chest leads, may be considered to suggest a delay in the activation of the posterobasal region of the left ventricle, the effects of which vary in different leads according to their orientation to the involved region. Thus, when Leads aV_L and I are more affected by the epicardial potentials of the involved portion of the left ventricle, the slurring would be expected to occur on the downstroke of the R wave. The late S waves in left chest leads cannot be explained by a transition zone effect since the latter occurs at Lead V_4. These S waves and the late slurred R in aV_R would tend to differentiate such cases from patterns of uncomplicated left ventricular strain. Although the QRS interval measures 0.12 second, the S-wave pattern, the R in aV_R, and the Q waves in aV_L and I tend to differentiate this from complete or incomplete BBB. Such patterns have been recently termed "posterocaudal arborization block"[35] and "S-type of peripheral left ventricular block,"[26] but the final acceptance of this interpretation needs confirmation.

When the region of defective peripheral conduction involves only a small and circumscribed area of the free wall of the ventricle, whether located in the inner or outer layer or throughout the free wall, it would be anticipated that only leads in closest proximity to the affected region would show the conduction defect.[31] Weinberg and Katz[37] recognized such a pattern in the anterior right ventricular wall and designated it a "focal right IV block." In contrast to the patterns of incomplete right BBB and diffuse peripheral right IV block in which the QRS prolongation is noted in all leads, the pattern of a focal right IV block is characterized by widening, slurring, decreased voltage, and a late "intrinsicoid" deflection limited to one or more of the right-sided chest leads and with no evidence of defective conduction in any other leads. We have encountered such records from time to time, the pattern apparently varying with the extent of the area involved and the presence of left or right ventricular strain. In Fig. 3, *B* a slurred M-shaped complex is found in Leads V_1 to V_3 in which the QRS interval is widened to 0.12 second compared to an interval of 0.08 second in the other leads. The late "intrinsicoid" deflection in these leads indicates the delay of right ventricular activation time; since the other leads do not display a similar QRS prolongation, an incomplete right BBB can be ruled out. However, it should be realized that tracings exhibiting the pattern of delayed activation only in certain right-sided chest leads can still represent extensive peripheral delay throughout the right ventricle in which the magnitude of the late right ventricular forces is such as to cause effects only in leads in close proximity to the right ventricle. In Fig. 3, *C* the left-sided chest leads are indicative of left ventricular strain. The rSr′ pattern in Lead V_2 is similar to that reported by Weinberg and Katz.[37] The r′ is inscribed significantly later than the forces expected incident to activation of the basal left ventricle; the widened QRS interval limited to V_2 and the late positive deflection in this lead only suggest a focal area of late activation in the free wall of the anterior right ventricle. Fig. 4, *A* and *E* present other instances of focal right IV block to which the same reasoning has been applied. Evidence of the focal nature of the conduction defect is found

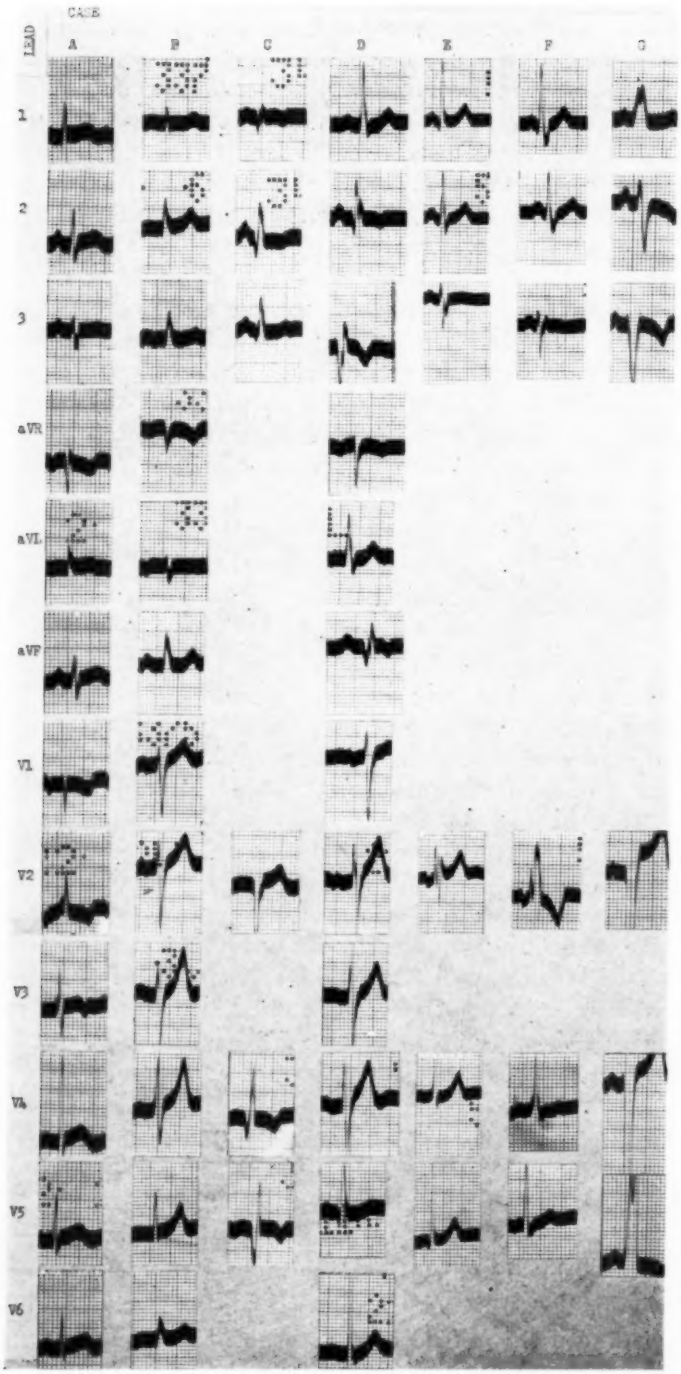

Fig. 4.—Different types of delay of intraventricular conduction. Case *A* had subacute pyelonephritis; Case *B* had obesity. Cases *C* and *D* had clinical evidence of remote confluent myocardial infarction. Cases *E* and *F* are records taken seven years apart on a patient with arteriosclerotic heart disease. Case *G* had hypertensive and arteriosclerotic heart disease. Discussed in text.

in Lead V_2; that this is not a transition zone effect is seen in Fig. 4, *A*, where S waves are present in V_1 and V_3 to V_6 but absent in V_2. In harmony with this concept is the recent demonstration that pressure by an intracardiac catheter against the endocardium of the right ventricle could elicit delayed activation of focal areas.[31]

The QRS complex of Lead V_1 in Case *D*, Fig. 3 resembles that of V_2 in Case *C*; however, evidence of the delayed activation is also manifested in other leads, either by a late slurred R′ or a late slurred S wave. The QRS interval throughout measures 0.10 second, and the pattern thus resembles that of complete right BBB. The pattern of Fig. 3, *E* resembles that of record *D*; *D* and *E* are closely similar to those patterns in which an incomplete right BBB has been demonstrated in instances of experimental BBB in the dogs[4] or during cardiac catheterization in man by pressure against the septum by an intracardiac catheter.[38] The major differences between records such as Fig. 3, *D* and *E* and patterns of complete right BBB are the lesser degree of QRS prolongation and the right-sided chest lead configuration; in incomplete right BBB the latter consists of an rSr′ complex in which there is a prominent S wave and a small or "embryonic" R′ deflection.[4] However, it is still conceivable that Cases *D* and *E* represent a peripheral conduction defect with the late forces produced by excitation of the right ventricle of such magnitude as to appear in every lead. We have not encountered definite instances of focal block in the left ventricle. A focal peripheral block involving the anterolateral region of the left ventricle is suggested by patterns such as Fig. 4, *B*, in which marked slurring, low voltage, and a later activation time are limited to Leads V_5 and V_7 of the precordial leads. On the other hand, this pattern may merely represent the normal late activation of the basal left ventricle and/or a greater distance between electrode and epicardium. A similar problem arises in distinguishing focal right IV block from patterns due to the normally late excitation of the conus region of the right ventricle.

Despite the evidence to the contrary,[9] careful investigations have demonstrated a slight asynchrony of activation of different parts of the epicardial surfaces, the posterobasal left ventricle and the conus region of the right ventricle being activated last;[24,39] indeed, critical methods have suggested that the conus region is activated at least as late and usually later than the basal left ventricle in mammalian hearts.[11] It is apparent, however, that the late activation of the conus could elicit a final positive deflection in right-sided chest leads if its time of activation occurred sufficiently late and particularly if the magnitude of the electrical forces created were large enough to appear in precordial leads. Thus, such an M-shaped rSr′ deflection might be normal.[24] The inscription of the final r′, its amplitude, and the number of leads in which it appears vary in accordance with the forces produced and the temporal relationship of the conus activation to that of the left ventricle. This probably explains why this final deflection is not observed in right precordial leads of many electrocardiograms. However, it is often encountered in one or more right chest leads in electrocardiograms obtained from normal persons. Fig. 3, *F*, *G*, and *H* illustrate such normal patterns and should be compared with records considered representative of incomplete right BBB (Fig. 3, *D* and *E*) or focal peripheral

right-sided IV block (Fig. 3, *B* and *C*). Case *F* shows the final small R deflection in Leads V_1 and V_2; in Case *G*, it is observed only in Lead V_1, and in Case *H* an "embryonic" equivalent of a second R wave in Leads V_1 and V_2 illustrates the same late conus activation. In contrast to the abnormal cases, the QRS interval in the latter three cases does not exceed that of other leads.

For various reasons,[30] the most extensive area of myocardial infarction is in the subendocardial region, and occasionally an infarct is limited to this layer and viable muscle may still be present in the outer layers of the ventricle. This is revealed in the electrocardiogram by wide, deep Q waves and late R waves in leads showing the epicardial potentials of the involved area. Fig. 4, *C* was obtained from a patient with an infarct of the anterolateral wall. An R wave is still inscribed in Leads V_4 and V_5 (and in the limb leads); the QRS interval measures 0.10 second, and the time of onset of the "intrinsicoid" deflection in these leads is 0.08 second, thus manifesting the delay in the activation of the lateral wall of the left ventricle. The peripheral conduction disturbance, in this instance, can thus be ascribed to actual infarction of the inner layers of the ventricular wall in this region. Figure 4, *D* presents a similar instance of focal delay in the posterior wall. The QRS interval measures 0.12 second in many leads, but the pattern of left BBB complicating posterior wall infarction[3] is not observed. A delay in the activation of the posterior wall of the subepicardial region is suggested by the late notching of the R waves in Leads aV_F, II, and III, the leads picking up epicardial potentials of the involved myocardium, and in the slurred S wave in the left chest leads, aV_L and I; the different pattern in the latter leads is again due to their different orientation to the involved part of the posterior wall. This record, where the lesion can be localized to the posterior wall and the region of delayed excitation to the outer layers of this part of the heart, lends credence to the explanation of similar patterns (Fig. 2, *H*) ascribed to peripheral delayed conduction in the subepicardium of the posterior wall of the left ventricle.

BUNDLE BRANCH BLOCK VERSUS "PERIPHERAL" INTRAVENTRICULAR BLOCK

In the previous discussion it has been pointed out that certain electrocardiographic patterns are most likely produced by abnormal impulse propagation in the ventricular walls. In some instances, as in a pattern of ventricular strain in which the QRS interval is widened to 0.10 or 0.12 second and when there is a delayed ventricular activation time (onset time of the "intrinsicoid" deflection), it is not easy to distinguish an element of delay in impulse transmission through the main bundle branches from a slow spread through the subendocardial network. Patterns caused by a bundle branch mechanism can be established from a comparison with patterns of BBB obtained experimentally or in cases where transeptal activation of the ventricle below the blocking lesion in the main bundle branch can be proved in human beings by intracardiac leads or in the presence of ectopic beats (Figs. 5 and 6). It remains therefore to discuss whether a peripheral conduction abnormality could produce patterns similar to those of BBB.

Previous studies[2] and our own observations have failed to clarify the latter problem satisfactorily. However, it would appear that the characteristic broad ventricular complex in left-sided precordial leads, consisting of a large bifid R wave with a deep apical notch (Figs 2, *A* and 4, *G*, Lead V_5), represents the pattern of left BBB. When this pattern is complicated by low voltages and when there is considerable slurring of the deflections (Fig. 2, *B*, *C*, and *D*), defective transeptal and/or peripheral IV conduction may be superimposed on a left BBB mechanism. When the voltage is small and marked slurring is present but the QRS interval is normal or only slightly widened, and when the basic bifid R-wave contour is absent, it would appear that one type of peripheral defective conduction without a BBB is present (Fig. 2, *F* and *G*). Other probable patterns of peripheral left and right IV conduction defects have been described already. It has never been satisfactorily demonstrated that a *peripheral* conduction defect alone could produce the basic pattern of left BBB (Fig. 2, *A*, V_5).

Three types of QRS deflections are commonly encountered in Lead I in cases of right BBB: These include a pattern of a slender R wave followed by a broad, slurred, but smaller S wave, the "S-type" (Fig. 1, *E* and *G*; Fig. 4, *F*); a small R wave followed by a slurred, broad, and deep S wave, the "uncommon type" (Fig. 1, *F*); and an "intermediate pattern," consisting of a more or less equiphasic RS complex (Fig. 1, *A* and *D*; Fig. 6, *B*).

It is generally agreed that the uncommon and intermediate types are due to a BBB, but there is disagreement in the case of the S-type. Electrocardiograms in which the S-type of block has appeared intermittently have shown that, except in right-sided chest leads, only the final part of the QRS deflection is altered with the appearance of the block pattern.[20] Vector analysis[40,41] has demonstrated an abnormal course of the vector loop only in its final portion and has led to the recent concept that the S-type of IV block is of peripheral origin rather than a BBB. We have encountered an interesting case in this regard. The electrocardiogram in Fig. 4, *E* is essentially normal except for Lead CF_2 in which a broadened triphasic complex can be noted with the late "intrinsicoid" deflection. There is also a significant widening of the QRS interval to 0.14 second in this lead but no evidence of a conduction defect in other leads. As discussed above, such a pattern represents a focal peripheral block in the right ventricle. Years later an S-type of block appeared in this patient's electrocardiogram (Fig. 4, *F*). In this case it is conceivable that the peripheral area of block had extended throughout the right ventricular wall in contrast to the previous focal lesion in the first record; its activation was now sufficiently delayed to permit late electromotive forces, incident to the activation of the right ventricle, also to be revealed in leads more distant from the epicardial surface of the right ventricle.

There is, however, no clear cut evidence that the S-type or one of the other patterns of right bundle branch block is caused by a peripheral conduction defect. Indeed, the available evidence tends to substantiate the BBB mechanism. Study of the published cases of right BBB in man, proved by intracavity leads, shows that the S-type, the uncommon type, and the mixed type can all be produced by a right BBB. These patterns have also been produced

in man during cardiac catheterization by pressure of the catheter against the right side of the IV septum.[31,32,38] In some instances, when the catheter was partly retracted but remained in the right ventricle, the pattern of right BBB disappeared; in one patient studied here whose electrocardiogram prior to catheterization was normal, an S-type block appeared and persisted for 30 minutes following entire withdrawal of the cardiac catheter. It is unlikely that pressure of the catheter upon certain peripheral subendocardial regions could have accounted for the appearance of the IV block and its persistence after the catheter was removed. Before the pattern of complete right BBB appeared in the continuous recording, QRS complexes of similar contour, but shorter in duration, were obtained and have to be consequently ascribed to an incomplete right BBB. The S-type of block appearing in young individuals as an isolated and apparently benign congenital anomaly of the conduction system[2] is most likely due to a BBB. In other cases in which the S-type of block has appeared transiently or intermittently, a peripheral conduction defect does not seem plausible.

The frequent association of patterns of IV block (BBB) with chronic cardiac enlargement and myocardial fibrosis has also been offered as proof of a "peripheral" origin of such patterns; further proof was believed to be shown by the production of such patterns by experimental acute intraventricular hypertension.[2] Instances where such patterns were present in patients in whom no histologic lesions of the bundle branches were found at necropsy[2] lent credence to this belief. However, the production of temporary BBB by mere pressure of a knife against the septum of the dog heart[2] and in human beings by the pressure of an intracardiac catheter demonstrates that BBB can be caused merely by pressure in the absence of organic blocking lesions. Furthermore, since extensive experimentally produced lesions throughout the subendocardium failed to lead to patterns of BBB, it is likely that increased intraventricular pressure, clinical or experimental, may have produced a BBB in these cases.

The mechanisms which might account for the variations in the pattern of right BBB in Leads I and V_1, which have been described previously, are not entirely clear. It might be suggestive to explain variations in Lead I by different "electrical" positions. However, the latter explanation accounts only for certain rather unusual variations of the limb lead patterns. When our electrocardiograms of right IV block were separated into groups according to the three patterns commonly encountered and described above, it was found that a variety of "electrical" positions was present in each group; the electrical position was thus found to have a minor role in causing the commonly observed patterns in Leads I and V_1. A consideration of the theoretical factors discussed above for instances of right and left IV block would suggest that hypertrophy and/or infarction of the septum and/or left and right ventricular wall may be the dominant factor in causing the varied patterns which have been described. This view has been expressed previously.[42,43]

Occasionally, indirect proof of the interruption of conduction through one of the main bundle branches can be established in instances where activation of the ventricles also occurs by impulses of ectopic origin. In Fig. 5 the beats of supraventricular origin (sinus beats) have the pattern of left BBB with a QRS

duration of 0.14 second. The QRS interval of premature beats of the S-type, present in every lead, is only 0.10 second. As pointed out previously,[8,44] this phenomenon can be explained by assuming an origin of the ectopic premature impulse in the IV septum below the site of the blocking lesion in the left main bundle. Thus, the ectopic impulse could reach both bundle branches simultaneously and produce, in contrast to a supraventricular impulse, a QRS of more

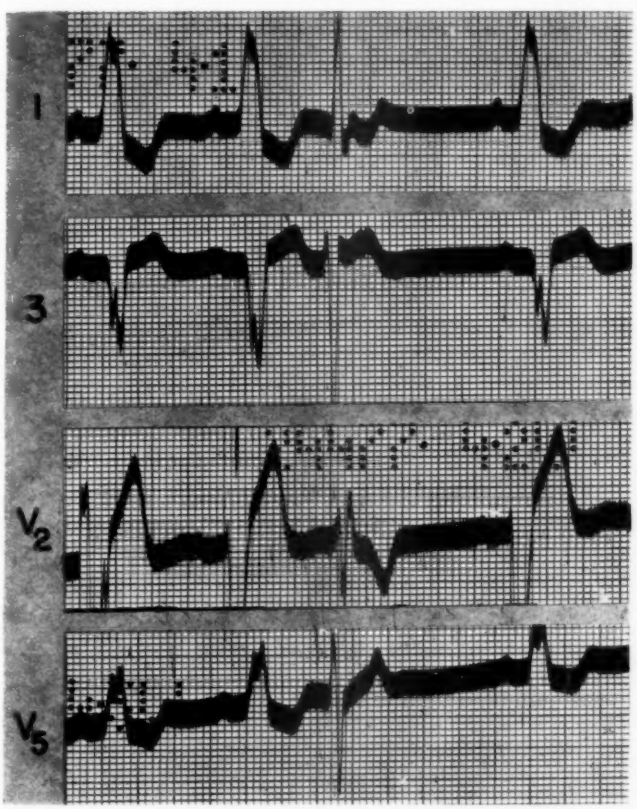

Fig. 5.—Premature beats with the pattern resembling S-type of right BBB in an instance of left BBB. Note that the QRS duration in premature beats (0.10 second) is shorter than that of the sinus beats (0.14 second). Discussed in text.

or less normal duration. In Fig. 5 the premature beats have the pattern of right BBB, pointing to an additional organic or functional conduction defect in the right ventricle distal to the point of origin of the premature beat. We are unable to decide (a) whether this is an instance of bilateral BBB, the left-sided lesion being located higher in the conduction system than the right-sided one, or (b) whether it is an instance of a combination of left BBB with a right-sided peripheral IV conduction defect, or (c) whether the premature impulse had its origin more to the left side of the septum below the region of block, thus reaching the left bundle earlier than the right one.

The mechanism producing the arrhythmia seen in Fig. 6 is described in its legend. This case bears a striking resemblance to patterns obtained by Wilson and Herrmann,[8] when the right ventricle of a dog was stimulated at various points in the spontaneous cardiac cycle after the right main bundle was cut. Various transitional complexes having patterns intermediate in form between those of right and left BBB were obtained, similar to those illustrated in Fig. 6, *B*.

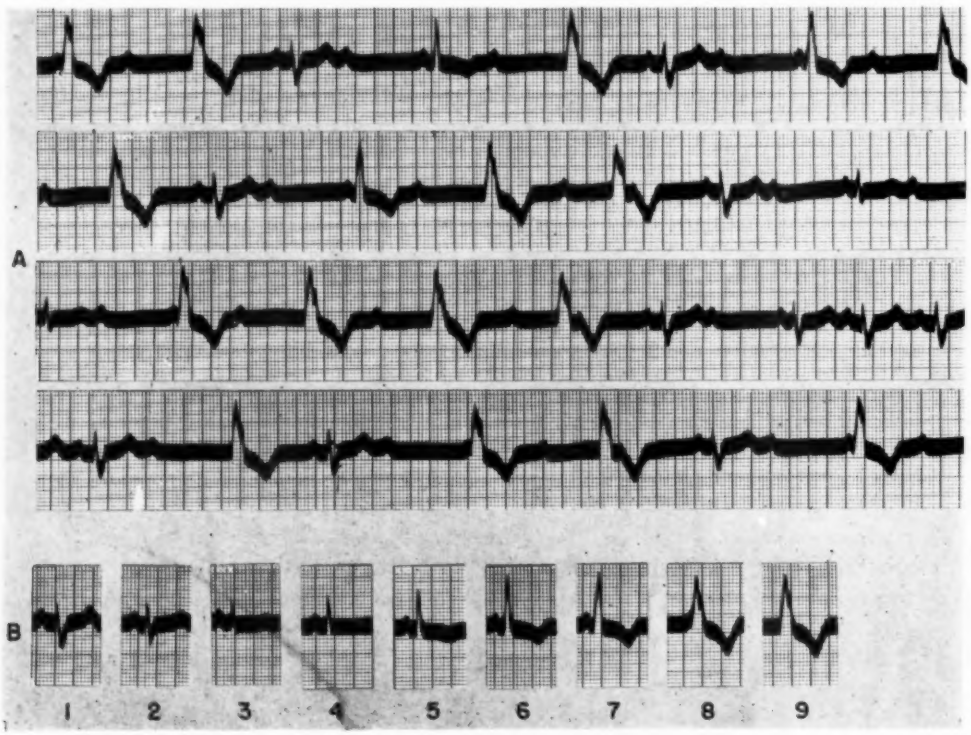

Fig. 6.—*A*, Continuous record of Lead I. The last beat in each strip is repeated as the first beat in the next strip. Sinus rhythm with second degree atrioventricular block is present. The P-R interval of conducted beats measures 0.20 second. The only instance where conduction occurs twice in succession can be seen at the end of the third strip. All conducted beats have the pattern of right BBB. When a P wave is blocked, an idioventricular pacemaker escapes in the ensuing long ventricular interval. In contrast to the conducted beats, it has the pattern of left BBB. In many instances, conduction of a sinus impulse occurs at the time of the appearance of the first idioventricular complex, thus giving rise to fusion beats of varying contour. The spacing between the beats of ectopic origin suggests the presence of a parasystolic pacemaker in the right ventricle discharging at a rate of 43 per minute.

B, The various types of fusion beats encountered in a long tracing taken in Lead I in the same case as *A* are illustrated. *1* is a conducted sinus impulse with a P-R interval of 0.20 second and right BBB. *8* and *9* are ectopic beats arising in the right ventricle. *1* to *7* represent the gradual transition between *1* and *9*, associated with a progressive shortening of the P-R distance. Discussed in text.

In the case presented, the following considerations seem to support the localization of the right-sided lesion in the main bundle branch: The contour of the idioventricular beats (Fig. 6, *B 9*) is characteristic of ectopic beats originating in the right ventricle. Hence, the appearance of fusion beats with normal QRS and normal P-R in the record would indicate that, at times, the left ventricle is activated by a sinus impulse conducted over an intact left bundle,

while the right ventricle is activated by the ectopic impulse located below the right-sided blocking lesion. However, if an ectopic right-sided impulse begins at a certain time prior to the inscription of the sinus impulse, it can penetrate into the septum and reach the left bundle before its activation by the sinus impulse (Fig. 6, *B 8*). The difference (0.04 second) between the shortest P-R distance preceding a fusion beat (0.12 second in Fig. 6, *B 7*) and the longest P-R distance preceding a pure ectopic beat (0.08 second in Fig. 6, *B 8*) indicates the maximal time for transeptal conduction of the ectopic impulse from the right ventricle to the left ventricle.* The evidence of transeptal activation of the left ventricle, preventing a fusion beat, substantiates a block of the sinus impulse in the main right bundle, and thus excludes, in this case, the localization of the IV conduction defect in the free wall of the right ventricle.

It is apparent from this study that the diagnosis of the location of conduction defects within the ventricles is still far from settled. Intracardiac leads have been shown to be ideally suited to study transeptal conduction[12] and thus to establish the existence or absence of a BBB mechanism in any given case. Extended studies with this technique, spatial vectorcardiography,[49] and careful anatomical and histological correlations will probably further clarify the problem of BBB and peripheral IV block. Until such time as complete clarification of this problem is obtained, the term left or right *bundle branch system block* seems more appropriate than that of *bundle branch block*; the latter is a restricted designation which includes only one type of intraventricular conduction abnormality.

SUMMARY AND CONCLUSIONS

1. The question of localization of an intraventricular conduction defect to the right or left side of the heart has been largely resolved, as evident from the literature. The problem that remains is to decide whether IV conduction defects located distal to the main bundle branches may change or imitate the pattern of a block in one of the main bundle branches.

2. One hundred electrocardiograms were studied, in which the presence of an intraventricular conduction defect was indicated by marked slurring and notching and/or a prolongation of the QRS interval over 0.12 second. These anomalies were found throughout twelve-lead electrocardiograms (standard leads, aV limb leads, and multiple chest leads from position V_1 to V_6) in most of the cases and were found to be present in single chest leads only in some of the tracings.

3. The present study could not solve the problem satisfactorily. However, by comparison with experimental data and with data on intracavity leads, both available in the literature, the following tentative conclusions were made:

a. The characteristic pattern of an uncomplicated block in one of the bundle branches appears to be a tall upright QRS complex with a smooth upstroke and downstroke and a marked apical notch or slurring, the latter contributing predominantly to the QRS prolongation present throughout

*The value of 0.04 second is in accord with the minimal time of delay of impulse conduction in a bundle branch, postulated previously by Wilson and Herrmann[18] as necessary for the appearance of the pattern of complete BBB in the dog's electrocardiogram.

the record. The S-T-T is usually opposite in direction to the upright QRS. In right BBB, this pattern is found typically in right-sided chest leads (V_{3R} and V_1) in the form of an rSR′. In left BBB a bifid R without Q and S is present in left-sided precordial leads.

b. A deviation from this typical pattern may consist in a decrease of voltage, marked slurring or notching on the upstroke and/or downstroke of the QRS, and in the form of concordant T waves. The changes of the QRS are believed to be due to additional conduction defects present either in the free walls of the ventricles, in the septum, or in both. In the presence of such a pattern, it is often impossible to distinguish between a peripheral IV block and a combination of peripheral block with BBB.

c. A pattern resembling in contour a bundle branch defect but in which the QRS duration does not exceed normal values appears to represent incomplete BBB due to a mere delay of impulse transmission down one of the main bundle branches.

d. When the QRS prolongation and slurring are limited to single chest leads, a focal peripheral conduction defect may be present in the area which is nearest to the electrode. A notching found only in the upstroke of the QRS would suggest a subendocardial location of the conduction defect, while a slurred or notched terminal part would suggest that the focal lesion is located in a circumscript subepicardial area. The latter patterns are found not infrequently in cases of myocardial infarction, which do not involve the whole thickness of the myocardium. Electrocardiograms showing the normal late activation of the basal parts of the ventricles can usually be differentiated from an abnormal focal delay of intraventricular impulse transmission.

e. A combination of BBB with heart strain is suggested if, together with the QRS prolongation and typical contour, unusually high amplitudes and/or S-T-T changes characteristic of ventricular strain are found.

4. "Electrical" position has a certain influence on the pattern of BBB in the standard leads but is not the only factor which determines the contour in these leads in a given case. Hypertrophy plus infarction in different parts of the heart may also be responsible for "atypical" electrocardiographic patterns of IV conduction defects.

5. Two examples are presented to illustrate how, in rare instances, an IV conduction defect can be localized to one of the main bundle branches with the help of ectopic beats.

6. The difficulties in many instances in the path of distinguishing conduction defects in the free walls of the ventricles from those in the main bundle branches may be overcome in the future by the use of intracavity leads and other methods. Until such time as the problem is solved, the term right or left bundle branch *system* block is suggested for the designation of such cases.

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REFERENCES

1. Rosenman, R. H., Silber, E. N., Katz, L. N., and Shorr, B.: The Value of the aV Limb Leads and the V Chest Leads (V_{4R} to V_7) in Routine Clinical Electrocardiography, Am. Heart J. **40**:573, 1950.
2. Rosenman, R. H., Pick, A., and Katz, L. N.: Intraventricular Block. a Review of the Literature, Arch. Int. Med. **86**:196, 1950.
3. Katz, L. N.: Electrocardiography, ed. 2, Philadelphia, 1946, Lea & Febiger.
4. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossman, C. E., Hecht, H. H., Cotrim, N., Menezes, R., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, Am. Heart J. **27**:19, 1944.
5. Lewis, T., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart: Part II. The Ventricles, Phil. Tr., Lond. **206**:181, 1915.
6. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle Branch Block, Am. Heart J. **7**:305, 1932.
7. Wilson, F. N., and Johnston, F. D.: The Form of the Electrocardiogram in Stroud's Diagnosis and Treatment of Cardiovascular Disease, ed. 2, Vol. 2, Philadelphia, 1950, F. A. Davis Company.
8. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**:153, 1920.
9. Abramson, D. I., and Jochim, K. E.: The Spread of the Impulse in the Mammalian Ventricle, Am. J. Physiol. **120**:3, 1937.
10. Fenichel, N. M.: An Analysis of the QRS Complex of the Electrocardiogram, Am. Heart J. **7**:514, 1932.
11. Harris, A. S.: The Spread of the Excitation in Turtle, Dog, Cat and Monkey Ventricles, Am. J. Physiol. **134**:319, 1941.
12. Sodi-Pallares, D., Thomsen, P., and Soberon, J.: New Contributions to the Study of the Intracavity Potential in Cases of Right Bundle Branch Block in the Human Heart, Am. Heart J. **36**:1, 1948.
13. Sodeman, W. A., Johnston, F. D., and Wilson, F. N.: The Q_1 Deflection of the Electrocardiogram in Bundle Branch Block and Axis Deviation, Am. Heart J. **28**:271, 1944.
14. Kissin, M., Ackerman, W., and Katz, L. N.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Bundle Branch Block in Man, Am. J. M. Sc. **186**:721, 1933.
15. Jones, A. M., and Feil, H.: The Effect of Posture Upon Axis Deviation in Human Bundle Branch Block, Am. Heart J. **36**:739, 1948.
16. Weinberg, S., Reynolds, R., Rosenman, R. H., and Katz, L. N.: Electrocardiographic Changes Associated With Patchy Myocardial Fibrosis in the Absence of Confluent Myocardial Infarction. To be published.
17. Barker, J. M., and Valencia, F.: The Precordial Electrocardiogram in Incomplete Right Bundle Branch Block, Am. Heart J. **38**:376, 1949.
18. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle Branch Block and the Refractory Period of the Heart of the Dog, Heart **8**:229, 1921.
19. Wilson, F. N.: Concerning the Form of the QRS Deflection of the Electrocardiogram in Bundle Branch Block, J. Mt. Sinai Hosp. **8**:1110, 1942.
20. Segers, M.: A nouvelle basis pour interpretation of ecgs normaux et pathologique, Acta Cardiol., Suppl. IV, 1948.
21. Oppenheimer, B. S., and Rothschild, M. A.: Abnormalities in the QRS Group of the Electrocardiogram Associated With Myocardial Involvement, Proc. Soc. Exper. Biol. & Med. **14**:57, 1916.
22. Smith, F. M.: Experimental Observations on the Atypical QRS Waves of the Electrocardiogram of the Dog, Arch. Int. Med. **26**:205, 1920.
23. Pruitt, R. D., Barnes, A. R., and Essex, H. E.: Electrocardiographic Changes Associated With Lesions in the Deeper Layers of the Myocardium, Am. J. M. Sc. **210**:100, 1945.
24. Gardberg, M., and Ashman, R.: The QRS Complex of the ECG, Arch. Int. Med. **72**:210, 1943.
25. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, ed. 4, New York, 1941, Paul B. Hoeber, Inc.
26. Wedd, A. M.: The Clinical Significance of Slight Notching of the R Wave of the Electrocardiogram, Arch. Int. Med. **23**:515, 1919.
27. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram, Advances Int. Med. **2**:1, 1947.
28. Rasmussen, H.: The Electrocardiogram in Aortic Insufficiency With Special Reference to the Development of the Left Bundle Branch Block Electrocardiogram, Acta Med. Scandinav. **118**:385, 1944.
29. Master, A. M., Kalter, H., Dack, S., and Jaffe, H. J.: The Relation Between Bundle Branch Block and Cardiac Enlargement, Am. Heart J. **20**:186, 1940.

30. Gubner, R., and Ungerleider, H. E.: Electrocardiographic Criteria of Left Ventricular Hypertrophy; Factors Determining the Evolution of the Electrocardiographic Patterns in Hypertrophy and Bundle Branch Block, Arch. Int. Med. **72**:196, 1943.
31. Kert, M. J., and Hoobler, S. W.: Observations on the Potential Variations of the Cavities of the Right Side of the Human Heart, AM. HEART J. **38**:97, 1949.
32. Goldman, I. R., Blount, S. G., Jr., Friedlich, A. L., and Bing, R. J.: Electrocardiographic Observations During Cardiac Catheterization, Bull. Johns Hopkins Hosp. **86**:141, 1950.
33. Cole, K. S., and Curtis, H. J.: Electric Impedance of the Squid Axon During Activity, J. Gen. Physiol. **22**:649, 1938-1939.
34. Sodi-Pallares, D., Barbato, E., and Delmar, A.: Relationship Between the Intrinsic Deflection and Subepicardial Activation: An Experimental Study, AM. HEART J. **39**:387, 1950.
35. Holzmann, M.: Klinische Elektrokardiographie, Zurich, 1945, Fretz and Wachsmuth.
36. Meyer, P., and Schmidt, C.: Étude electrocardiographique de blocs localisés dans certaines régions du ventricule gauche (blocs focaux) en particulier de syndromes représentant l'homologue du bloc de Wilson pour le ventricule gauche, Arch. d. mal. du coeur **11**:707, 1948.
37. Weinberg, H. B., and Katz, L. N.: Two Unusual Types of Electrocardiograms, AM. HEART J. **19**:519, 1940.
38. Unpublished observations.
39. Nahum, L. H., and Chernoff, H. M.: The Spread of Excitation and the Order of Repolarization in the Human Heart, Federation Proc. **8**:117, 1949.
40. Vastessaeger, M.: Les troubles de la conduction intraventriculair chez l'homme, Acta Cardiol., Suppl. I, 1946.
41. Cabrera, E.: Basis electrophysiologiques de l'electrocardiographie applications cliniques, Paris, 1948, Masson & Cie.
42. Bayley, R. H.: The Frequency and Significance of Right Bundle Branch Block, Am. J. M. Sc. **188**:236, 1934.
43. Pick, A.: Beitrag zur Frage des atypischen Schenkelblocks, Ztschr. f. klin. Med. **129**:719, 1936.
44. Simon, A. J., and Langendorf, R.: Intraventricular Block With Ectopic Beats Approaching Normal QRS Duration, AM. HEART J. **27**:345, 1944.
45. Panbridge, J. F., Abildskov, J. A., Burch, G. E., and Cronwich, J. A.: A Study of the Spatial Vectorcardiogram in Left Bundle Branch Block, Circulation **1**:893, 1950.

THE TRANSITION ZONE IN PRECORDIAL ELECTROCARDIOGRAMS FROM MULTIPLE SITES

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PREVIOUS studies from this department have stressed that the surface of the precordium represents a manifestation of the electrical field created by the heart with a positive and negative area and a zone of transition between, which differ in distribution during the heart cycle.[1] The region in the serial precordial electrocardiogram commonly known as the transition zone has been the object of relatively little attention. Electrodes placed on the right precordium usually record mainly inverted QRS complexes and upright or inverted T waves, and those on the left precordium record mainly upright QRS and T-wave complexes. Between these two areas lies a region in which QRS complexes intermediate in form are recorded. Ordinarily, the transition zone has been considered for the QRS complex as a unit and for the T wave as such. The variable location and width of this region has remained somewhat of an enigma[7] and prompted this study. The region of transitional QRS complexes has also been correlated in this study with changes in T-wave direction and contour in the several leads.

MATERIAL STUDIED AND METHODS EMPLOYED

The transition zone was studied in 150 normal electrocardiograms and in 195 tracings exhibiting left, right, or combined ventricular strain. In each instance the records were grouped according to the "electrical" position.[7] The electrocardiograms were largely obtained during previous studies[2,3] and included the standard and aV limb leads and precordial leads V_1 to V_7, V_{3R}, and V_{4R}. The leads which marked the transition zones of both QRS complexes and T waves were noted in each instance. The QRS transition zone was defined in this study as the lead or leads in which approximately equiphasic RS waves were observed or as the position at which the QRS complex changed from a mainly inverted to a mainly upright complex, or vice versa. A T-wave transition zone was denoted by a change in its direction from inverted to upright, or vice versa. In certain instances, two transition zones were obtained for both QRS complexes and T waves.

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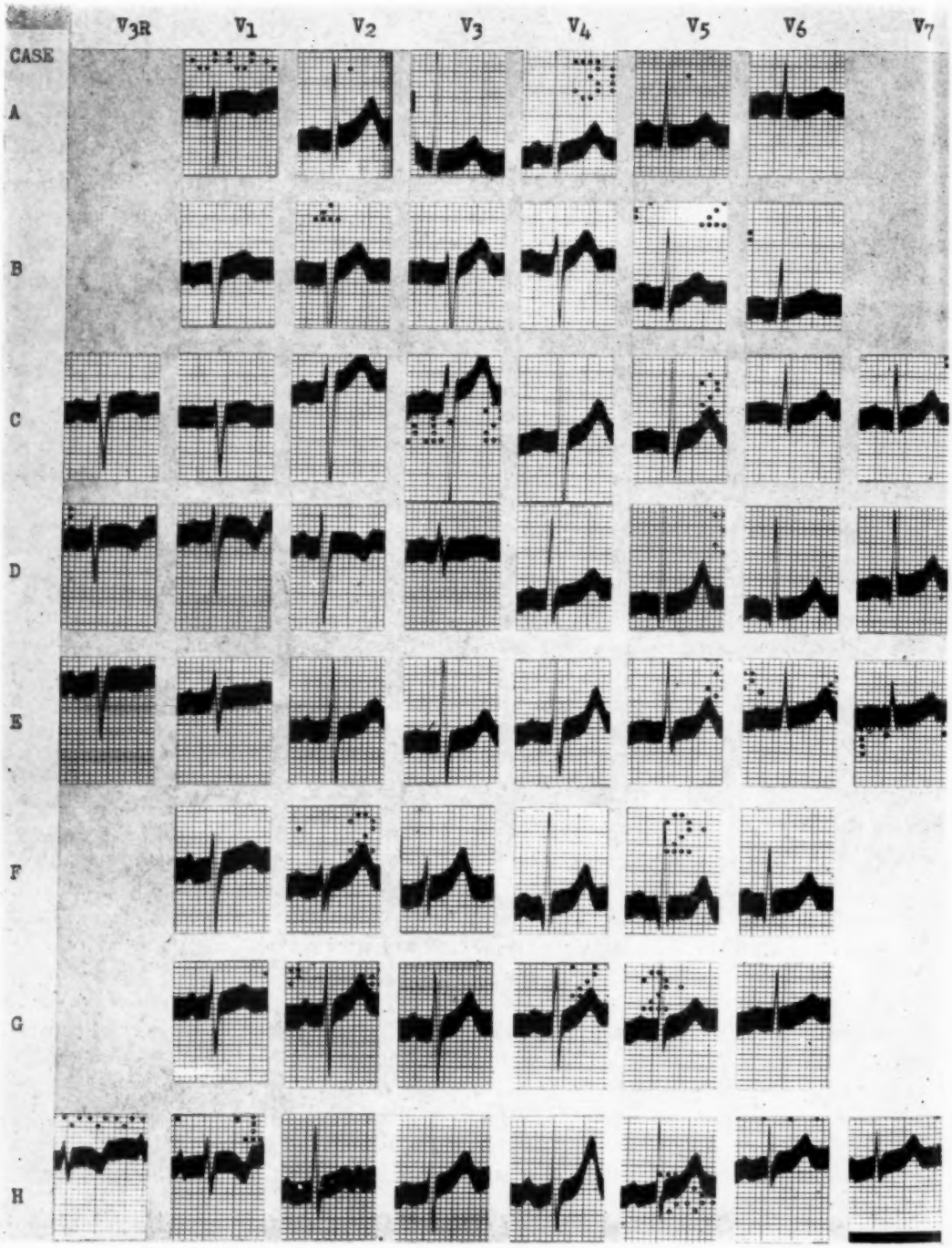

Fig. 1.—Various types of transition zones in normal precordial leads. The transition zone is abrupt in records *A* and *B*: a transitional complex can be seen in one lead in *C* and *D*, in two leads in *E* and *F*, and in three leads in *G*. The transition zone is shifted to the right in records, *A*, *F*, and *H* and to the left in *B*; it was most frequently found between positions 2 and 4 (records *C* and *D*). Prominent notched and slurred QRS deflections were characteristically found in transitional zones (*D* and *F*), and such complexes were often smaller than their neighboring deflections (*D*, *F*, and *H*). A notched T wave was occasionally noted in transitional regions (*D* and *H*).

The normal electrocardiograms were obtained from adults. Electrocardiograms with heart strain patterns were obtained from both adults and children. However, no records were included from children below 2 years of age. The criteria for diagnosis were those previously set forth.[3,7,8,9,12]

RESULTS

The transition zone varied in width and location in the 150 normal tracings (Table I), as has been previously noted.[7-9] The transition from a mainly inverted to mainly upright complex was sometimes abrupt (Fig. 1,*A* and *B*) with no transitional complex present; an intervening lead might have displayed an equiphasic RS complex in many such cases. In others, transitional, equiphasic RS complexes were encountered in one (Fig. 1,*C* and *D*), two (Fig. 1,*E* and *F*), and occasionally three (Fig. 1, *G*) leads. The usual location of the transition zone was between positions C_2 and C_4 (Fig. 1, *C* and *D*), although occasionally it was found shifted farther to the right (Fig. 1, *A*, *F*, and *H*) or left precordium (Fig. 1, *B*). There was a tendency for a more abrupt transition in "electrically" vertical and semivertical hearts and for a left-sided shift (clockwise) in vertical hearts. In other respects the character of the transition zone was essentially similar in all of the different electrical positions.

TABLE I. THE LOCATION AND WIDTH OF THE QRS TRANSITION ZONE IN VARIOUS ELECTRICAL POSITIONS IN NORMAL ELECTROCARDIOGRAMS

ELECTRICAL POSITION	NO. CASES	LOCATION AND WIDTH OF TRANSITION ZONES (T.Z.)				
			ABRUPT T.Z.*	T.Z.1†	T.Z.2†	T.Z.3†
Horizontal	30	No. Cases	10	16	2	2
		Location*	V_1–V_4	V_1–V_4	V_4–V_5	V_2–V_6
		Average location	V_3	V_3–V_4	V_4–V_5	V_3–V_5
Semihorizontal	30	No. cases	13	15	2	—
		Location	V_1–V_5	V_2–V_4	V_2–V_4	—
		Average location	V_2–V_4	V_2–V_3	V_3	—
Intermediate	30	No. cases	13	16	1	—
		Location	V_2–V_4	V_2–V_4	V_2–V_3	—
		Average location	V_3	V_3	V_2–V_3	—
Semivertical	30	No. cases	16	14	—	—
		Location	V_2–V_5	V_2–V_4	—	—
		Average location	V_3	V_3	—	—
Vertical	30	No. cases	17	13	—	—
		Location	V_2–V_5	V_2–V_5	—	—
		Average location	V_3–V_4	V_3–V_4	—	—

*Transition abrupt from mainly inverted to mainly upright complex.
†T.Z.1 = Transitional complex in one lead, T.Z.2 in two leads, T.Z.3 in three or more leads.

Prominent notching and slurring of QRS deflections were commonly encountered in transitional complexes (Fig. 1, *D* and *F*), and the latter were often of considerably smaller amplitude than those to either side (Fig. 1, *D*, *F*, and *H*),

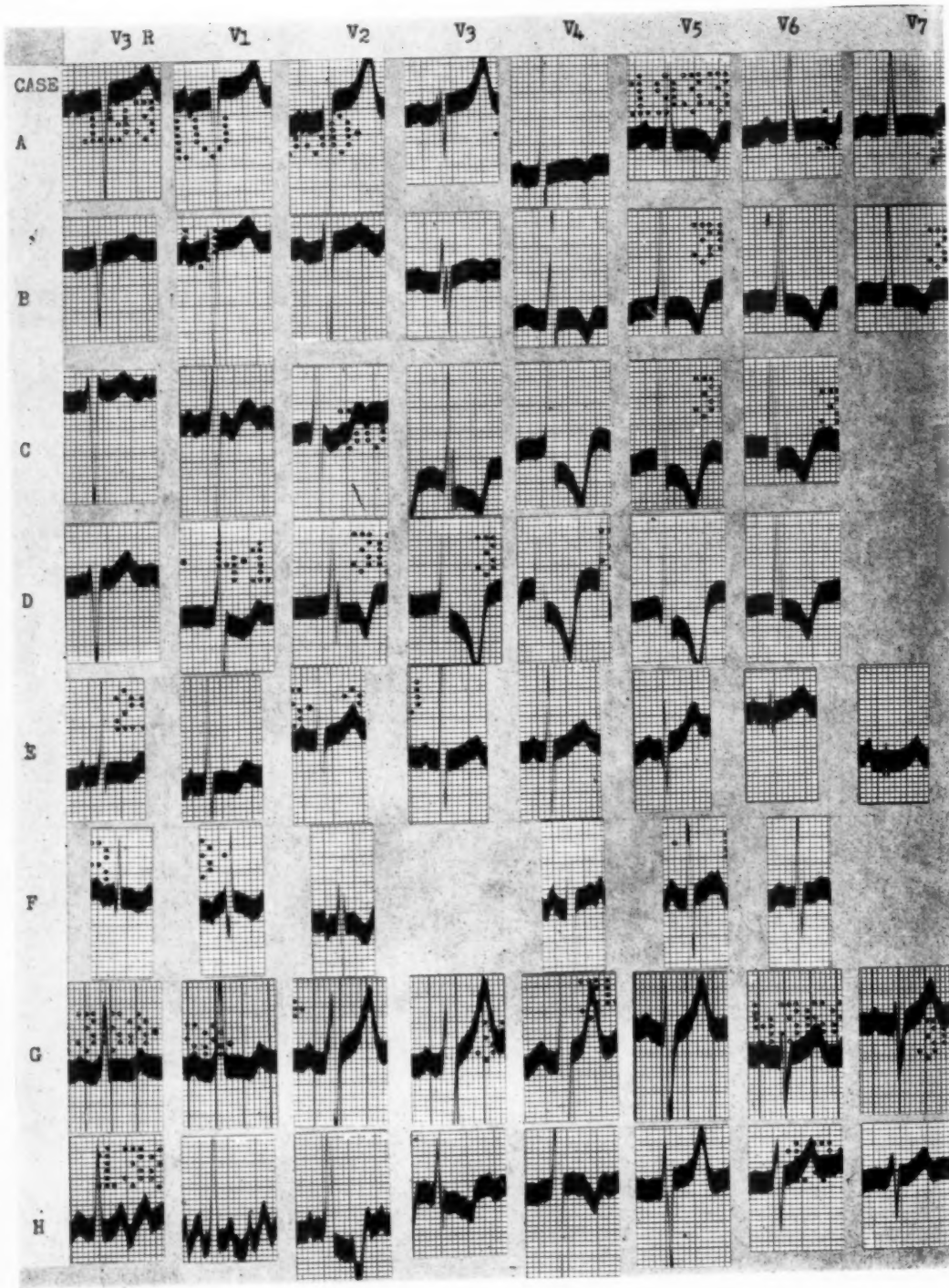

Fig. 2.—*(For legend see opposite page.)*

as previously noted.[7-9] A bizarre complex of this type was rarely observed in more than one lead.[9] The T-wave pattern was also essentially similar in all electrical positions. Upright T waves were frequently noted in all leads (Fig. 1, *B*, *C*, *F*, and *G*), and in others, a small inverted T wave was present in Leads V_{4R}, V_{3R}, and/or V_1 (Fig. 1, *A*, *D*, *E*, and *H*); on occasion, an inverted T wave was noted in Lead V_2 as well (Fig. 1, *D*), especially if the transition zone was shifted significantly toward the left. The T-wave transition in such cases often differed in position from that of the QRS complex transition. No instance was encountered in which there was an inverted T wave in one of these leads and upright T waves in the leads to the right of that position. Significant notching of the T wave was frequently observed in one and occasionally two of the leads in the transition zone (Fig. 1, *D* and *H*).[8]

The QRS complex transition zone in tracings exhibiting left ventricular strain (Table II) generally resembled that of the normal group. It was occasionally shifted far to the right (Fig. 2, *D*) or left but was most often noted at positions C_3 to C_4 (Fig. 2, *A* and *B*). There was a slight tendency for a transition to the left in vertical positions, and the transition zone never extended to the left of position V_5 in horizontal hearts. The T wave was sometimes notched in the region where its direction changed (Fig. 2, *B* and *C*). When the pattern of left ventricular strain was marked, the T waves were usually upright in the right chest leads and inverted in the left chest leads (Fig. 2, *A* and *D*). The change in T-wave direction was usually abrupt (Fig. 2, *A*) but occasionally occurred over a span of one or two leads (Fig. 2, *B*, *C*, and *D*). The location of this change was related to the position of the QRS complex transition zone, but the T-wave transition often occurred one position to the right or left of that of the QRS complex transition. Because of this, QRS complexes might be almost entirely inverted in all but two or three left chest leads; the presence of an inverted T wave in one or two leads with inverted QRS complexes to the right of the transition zone occasionally suggested anterior wall infarction. The presence of multiple chest leads is important in differentiating left ventricular strain in such instances. For no apparent reason the transition zone occasionally varied in successive records obtained from the same patient at different times (Fig. 2, *C* and *D*).

The transition zone in tracings exhibiting right ventricular strain differed from that of the previous groups. The electrical position was either vertical or horizontal in the thirty-five records studied (Table III). When the pattern of right ventricular strain was apparently not marked, the only abnormality consisting of a tall R wave and late "intrinsicoid" deflection in the right chest leads, mainly upright complexes were also observed in the left chest leads;

Fig. 2.—Various types of transitional regions occurring in tracings exhibiting left ventricular strain (records *A* to *D*); the transition zone was occasionally shifted to the right (*D*) or left, but usually found at positions 3 and/or 4 (*A* and *B*). Notched T waves were often observed in the lead where the direction of the T wave changed (*B* and *C*); the change in T-wave direction was usually abrupt (*A*) but occasionally spanned one or two leads (*B*, *C*, and *D*).

Tracings exhibiting right ventricular strain are shown in records *E* to *H*. Two QRS transition zones were often noted in such records (*F*). In tracings with patterns of apparently more advanced ventricular strain, the transition from mainly upright to mainly inverted complexes occurred abruptly (*H*) or was broad with transitional complexes occupying three or more leads (*E* and *G*). Different QRS and T-wave transitional zone positions can be noted in *F* and *H*.

TABLE II. THE LOCATION AND WIDTH OF THE QRS TRANSITION ZONE IN VARIOUS ELECTRICAL POSITIONS IN ELECTROCARDIOGRAMS EXHIBITING LEFT VENTRICULAR STRAIN

ELECTRICAL POSITION	NO. CASES	LOCATION AND WIDTH OF TRANSITION ZONES (T.Z.)				
			ABRUPT T.Z.*	T.Z.1†	T.Z.2†	T.Z.3†
Horizontal	30	No. cases	15	15	—	—
		Location*	V_2–V_5	V_1–V_4	—	—
		Average location	V_3–V_4	V_3–V_4	—	—
Semihorizontal	30	No. cases	15	15	—	—
		Location	V_2–V_5	V_2–V_5	—	—
		Average location	V_3–V_4	V_3–V_4	—	—
Intermediate	30	No. cases	13	14	3	—
		Location	V_2–V_6	V_2–V_4	V_2–V_4	—
		Average location	V_3–V_4	V_3	V_3	—
Semivertical	30	No. cases	14	14	2	—
		Location	V_2–V_5	V_3–V_5	V_1–V_3	—
		Average location	V_3–V_5	V_3–V_4	V_2	—
Vertical	30	No. cases	19	8	2	1
		Location	V_2–V_6	V_3–V_5	V_2–V_4	V_1–V_3
		Average location	V_3–V_5	V_4	V_3	V_1–V_3

*Transition zone abrupt, no transitional complex present.
†T.Z.1 = Transitional complex in one lead, T.Z.2 in two leads, T.Z.3 in three or more leads.

diphasic QRS complexes consisting of smaller R waves and deeper S waves were noted in one or more intervening leads. It is apparent that, in such records, two QRS complex transition zones were present (Fig. 2, *F*). The electrical position was usually vertical in such instances, and the T waves were either upright in all leads or inverted in those right-sided chest leads having tall R waves. When the pattern of right heart strain was apparently more advanced, as shown by a

TABLE III. THE LOCATION AND WIDTH OF THE QRS TRANSITION ZONE IN VARIOUS ELECTRICAL POSITIONS IN ELECTROCARDIOGRAMS EXHIBITING RIGHT VENTRICULAR STRAIN

ELECTRICAL POSITION	NO. CASES	LOCATION AND LEADS WITH TRANSITIONAL COMPLEXES*					
			ABSENT T.Z.†	T.Z.2‡	T.Z.2	T.Z.1	ABRUPT T.Z.
Horizontal	11	No. cases	1	4	2	2	2
		Location	—	V_1–V_6	V_1–V_3	V_3–V_6	V_{3R}–V_2
		Average location	—	V_3–V_5	V_2–V_3	V_4–V_5	V_1
Vertical	24	No. cases	1	6	1	4	12
		Location	—	V_1–V_5	V_1–V_2	V_1–V_3	V_{3R}–V_2
		Average location	—	V_2–V_4	V_1–V_2	V_2	V_1

*Code as in Tables I and II.
†No transition present in the leads employed in this study.
‡All leads have similar QRS complexes.

complete reversal in the normal right to left R/S ratio across the precordium,[12] a transition from mainly upright to mainly inverted complexes was noted (Fig. 2, *G* and *H*). The electrical position in such instances was usually horizontal. Inverted T waves were noted in Leads V_{4R} to V_2 or V_3 and were usually upright in the remaining leads (Fig. 2, *F* and *H*). In some instances of apparently advanced right ventricular strain, the transitional complexes were found in three or four leads, causing a broad transition zone (Fig. 2, *E* and *G*); leads to their right consisted of tall R waves and to their left of mainly inverted QRS complexes. The transition zones of QRS complexes and of T waves again often differed in position (Fig. 2, *F* and *H*) in each of the different types of patterns.

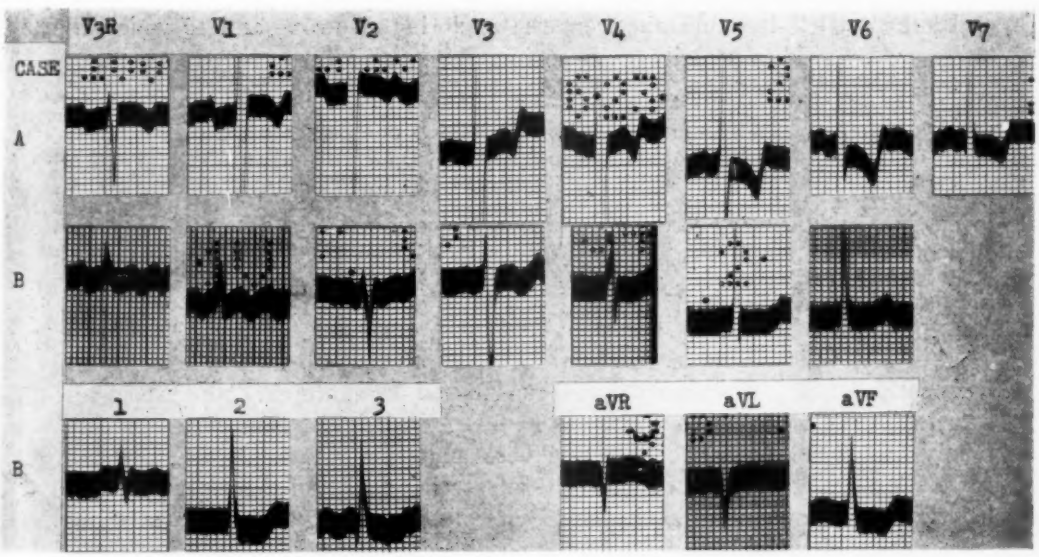

Fig. 3.—Two instances believed demonstrative of combined ventricular strain (see text). A double transition zone is usually noted in such cases.

Ten records were studied in which there was evidence of combined ventricular strain.[5] In such records abnormalities indicative of left ventricular strain often consisted of tall R waves and characteristic S-T-T changes in the left chest leads (Fig. 3, *A*); evidence of right ventricular strain consisted of late, tall R waves and inverted T waves in right chest leads (Fig. 3, *A*). Intervening leads displayed more or less equiphasic QRS complexes with small R waves and deep S waves and with upright or diphasic T waves (Leads V_3 and V_4, Fig. 3, *A*). It is apparent that in such records a double transition zone of both QRS completes and T waves is present. In other cases, left ventricular strain was apparent in the limb leads and right ventricular strain in the precordial leads (Fig. 3, *B*). A double transition zone (Leads V_1 to V_2 and V_4 to V_5, Fig. 3, *B*) was again noted in such cases, since intervening leads again displayed smaller upright and larger inverted deflections than leads to their left or right.

DISCUSSION

A lead obtained from an extracardiac point such as the chest wall reflects in varying degree the potential variations of every part of the heart; however, the magnitude of influence of any given element varies inversely as the square of its distance from the exploring electrode. Thus, empirical studies have shown that most of the chest leads ordinarily record complexes closely resembling those of direct epicardial leads obtained at corresponding positions.[7] Transitional QRS complexes in precordial leads are similar to those in direct epicardial leads recorded over or in the close vicinity of the interventricular septum. They represent more or less of a "mixture" of the deflections recorded in leads to the right or left of this region, i.e., the potential variations of those parts of the right and left ventricle least distant from the exploring electrode and to which the latter are believed to contribute approximately equally.[7]

The transition zone was found to vary rather widely in extent and location in all of the records studied. Transitional QRS complexes were often grossly notched or slurred and smaller in amplitude than those in leads to their right and left. The transition from upright to inverted T waves or vice versa, particularly in tracings exhibiting ventricular strain, often occurred in a different lead than that of the QRS transition. T waves in leads displaying transitional complexes were not uncommonly grossly notched in the normal records,[8] contrary to previous beliefs.[12,13]

An anatomic clockwise rotation (viewed from the apex) on the long axis frequently occurs in vertically placed hearts and an anatomic counterclockwise rotation in horizontally placed hearts.[14,16] Left ventricular enlargement is commonly associated with a counterclockwise anatomic rotation.[11] An excellent correlation has been found between the anatomic position of the septum and the location of the transition zone in the precordial leads.[11] Accordingly, a transition zone to the left would be frequently expected in electrically vertical hearts and a transition zone to the right in electrically horizontal hearts. In this study, except for a slight tendency in this direction, the width and location of the transition zone were not consistently affected by the electrical rotation on an anteroposterior axis. This apparent discrepancy may be explained in part by the "nature and extent of the distribution of good and poor electrical conductors in the conducting system within the ventricles, and the rate and sequence of impulse spread."[15] However, since the position of the septum and of the transition zone of precordial leads is well correlated,[11] it is likely that the factors mentioned above are of lesser importance in this regard. Of greater importance is the fact that the heart, electrically as well as anatomically, is subject to rotation on three axes.[10] These include (a) clockwise or counterclockwise rotation on the longitudinal axis, (b) rotation of the apex in a forward or backward direction on a transverse axis, and (c) rotation from the vertical to horizontal on an anteroposterior axis. Rotations on the three axes may vary simultaneously, being influenced by extracardiac as well as intrinsic factors. Thus, it has been shown that the anatomic position of the heart has no constant effect on the position of the interventricular septum.[11]

The character and width of the transition zone probably primarily depend on the angle made by the septum with the anterior chest wall. When the septum is perpendicular to the line of the precordial leads used, an abrupt QRS transition might be expected; when the septum is markedly deviated from the perpendicular to the line of the precordial lead used, a broad and more gradual transition zone might be expected.[8]

The broad transition zone that is often observed in tracings exhibiting right ventricular strain can be ascribed partly to the more complicated balance of potentials developed during the activation of the left and right ventricles as well as to the tendency in such hearts for the septum to be in a plane markedly deviated from the perpendicular to the line of the precordial leads used. The position of the septum is related more to the type of rotation present than to the actual right ventricular enlargement;[8,11,14,16] in this regard, a backward shift of the apex probably plays an important role.[8]

The location and width of the transition zone were found of little diagnostic value as isolated criteria in the interpretation of ventricular strain, a reflection of the finding that ventricular enlargement has no consistent effect on the anatomic position of the septum.[11] However, a "double" transition zone up to now has been found only in electrocardiograms exhibiting right or combined ventricular strain. Multiple precordial leads are frequently necessary to cross the transition zone.

SUMMARY

The transition zone of QRS complexes and of T waves in multiple precordial leads (V_{4R} to V_7) has been studied in 150 normal adult electrocardiograms and in 195 tracings exhibiting left, right, or combined ventricular strain in various electrical positions. Transitional QRS complexes often displayed prominent slurring, notching, and deflections of smaller amplitude than neighboring complexes. Transitional T waves were often prominently notched, even in normal electrocardiograms. The QRS complex transition zone often differed significantly in position from that of transitional T waves.

The transition zone varied widely in width and location, both in normal records and in those exhibiting patterns of ventricular strain. This variability was poorly correlated with the electrical position, although there was a tendency for a late transition zone in vertical positions. The various factors involved in determining the variable width and location of the transition zone have been briefly discussed.

The location and width of the transition zone were found to be of little diagnostic value as isolated criteria in the interpretation of left or right ventricular strain. However, a double transition zone was noted only in tracings exhibiting right or combined ventricular strain in the precordial leads.

We are indebted to Dr. L. N. Katz for his suggestions.

REFERENCES

1a. Bohning, A., Katz, L. N., Robinow, M., and Gertz, G.: The Value and Significance of Multiple Chest Leads in Man: I. Normal and Hypertrophied Hearts, AM. HEART J. **18**:25, 1939.

1b. Katz, L. N.: Concerning a New Concept of the Genesis of the Electrocardiogram, AM. HEART J. **13**:17, 1937.

2. Rosenman, R. H., Silber, E. N., Katz, L. N., and Shorr, B.: The Value of the aV Limb Leads and the V Chest Leads (V_{4R} to V_7) in Routine Clinical Electrocardiography, AM. HEART J. **40**:573, 1950.

3. Rosenman, R. H., Krause, S., Hwang, W., and Katz, L. N.: The Electrocardiographic Diagnosis of Combined Left and Right Ventricular Strain. To be published.

4. Wolferth, C. C., and Livezey, M. M.: Observations on Changes in Ventricular Complex Produced by Bundle Branch Block With Special Reference to the Hypothesis of Electrical Axis and the Concept of the Dextrocardiogram and Levocardiogram, AM. HEART J. **34**:1, 1947.

5. Wilson, F. N.: The Form of the Electrocardiogram: In Stroud's Diagnosis and Treatment of Cardiovascular Disease, ed. 1, Vol. 1, Philadelphia, 1940, F. A. Davis Company.

6. Gardberg, M., and Ashman, R.: The QRS Complex of the Electrocardiogram, Arch. Int. Med. **72**:210, 1943.

7. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram, Advances Int. Med. **2**:1, 1947.

8. Myers, G. B., Klein, H. A., Stofer, B. E., and Hiratzka, L.: Normal Variations in Multiple Precordial Leads, AM. HEART J. **34**:785, 1947.

9. Sokolow, M., and Friedlander, R. D.: The Normal Unipolar Precordial and Limb Lead Electrocardiogram, AM. HEART J. **38**:665, 1949.

10. Goldberger, E.: Unipolar Lead Electrocardiography, ed. 2, Philadelphia, 1949, Lea & Febiger.

11. Rosenberg, M. J., and Agress, C. M.: Position of Precordial Leads: An Anatomical Study, AM. HEART J. **38**:593, 1949.

12. Katz, L. N.: Electrocardiography, ed. 2, Philadelphia, 1946, Lea & Febiger.

13. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, ed. 4, New York, 1941, Paul Hoeber, Inc.

14. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, ed. 2, Springfield, Ill., 1943, Charles C Thomas, Publisher.

15. Katz, L. N.: Clinical Electrocardiography: Its Present Position and Possible Potentialities, Circulation. In press.

16. Schwedel, J. B.: Clinical Roentgenology of the Heart, New York, 1946, Paul B. Hoeber, Inc.

ELECTROCARDIOGRAPHIC CHANGES IN FUNNEL CHEST

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STUDIES of the heart in patients with funnel chest by various observers[1-6] revealed only insignificant changes of the electrocardiogram: high P waves in Leads II and III, a tendency to right axis deviation, and occasionally a left axis deviation. Few of the investigations included an apical chest lead. Teplick and Drake[2] described "minor variations" in Lead CF_4 which most constantly affected the T waves; there was elevation of the S-T segment, and the T waves were either low or diphasic or inverted. In one patient the electrocardiogram (their Fig. 11) included multiple precordial leads and showed inverted or diphasic T waves in Leads CF_2 through CF_5.

Our interest in this subject was aroused by the observation of a patient with funnel chest who complained of vague precordial pain. He had been confined to bed because of the finding of sharply inverted T waves in multiple precordial leads which were interpreted as signs of myocardial ischemia. We then studied thirteen patients with funnel chest, the majority of which presented similar findings in the electrocardiogram (Table I). Precordial unipolar leads were taken in addition to the standard limb leads in all patients with the exception of one, in whom CF leads were obtained. Augmented unipolar limb leads were available in all cases but one. The age of the patients ranged from 11 to 66 years; two patients were of juvenile age, 11 and 15 years old. There were ten female and three male patients.

CASE REPORTS

CASE 1.—S. S., a 39-year-old man, was first examined on Nov. 27, 1947. For the past five years he had suffered from insomnia and fatigue. In 1942 and 1943, he complained for short periods of time of precordial pain which he attributed to "gas." He never experienced distress in the chest in association with walking or climbing stairs. In July, 1947, the patient felt "heaviness" in the "heart" region, but his capacity for effort was unimpaired. An electrocardiogram showed sharply inverted T waves in multiple leads from the right side of the precordium, and therefore the patient was ordered to rest in bed. The complaints subsided after the patient was advised by another physician that he could return to work. In November, 1947, he consulted one of us because of pinching pain in the left arm.

On physical examination, a deep funnel depression of the chest was noted, occupying the lower two-thirds of the sternum and adjacent portions of the ribs in an area about 3 cm. wide bilaterally. The external anteroposterior diameter of the chest at the level of the deepest sternal depression measured slightly less than 16 cm. Examination of the lungs revealed no abnormal findings. The apical thrust of the heart was not palpable. The heart sounds were of fair quality in the apical region and muffled at the base of the heart. No murmurs were heard. The heart

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TABLE I. CHANGES OF THE ELECTROCARDIOGRAM IN PATIENTS WITH FUNNEL CHEST

CASE NO.	AGE	ANTEROPOSTERIOR DIAMETER OF CHEST AT THE LEVEL OF DEEPEST DEPRESSION		ELECTROCARDIOGRAPHIC FEATURES
		EXTERNAL (CM.)	INTERNAL (CM.)	
1	39	16		Intermediate position; inversion of T in Leads V_1 through V_3
2	44	13.5		Vertical position; inversion of T in Leads V_1 through V_3
3	48	10	0.5	Vertical position; inversion of T in Leads I and V_1 through V_4
4	63	12.5		No axis deviation; inversion of T in Leads CF_1 through CF_3
5	54	16	11	Intermediate position; inversion of T in Leads V_1 and V_2; notching of T in Leads V_3 and V_4
6	66	12.25		Semihorizontal position; inversion of T in Leads V_1 through V_3
7*	47	18.5		Intermediate position; inversion of T in Leads V_1 and V_3; notching of T in Leads V_2 and V_4
8	35	18	9.8	Vertical position; notching of T in Lead I; inversion of T in Leads V_1 through V_3; notching of T in Lead V_6
9	36	12.7		Intermediate position; inversion of T in Lead V_1, flat T in Lead V_2, low T in Lead V_3
10	43	13	6.3	Horizontal position; inversion of T in Lead V_1, upright T in other chest leads
11	26	17	8.5	Semivertical position; diphasic T in Lead V_1, upright T in other chest leads
12	11	12	5	Vertical position; inversion of T in Leads V_1 and V_2; notching of T in Lead V_3
13	13	12.5	4.4	Semihorizontal position; inversion of T in Leads V_1 through V_2. Following surgical repair, the T wave in Lead V_3 became upright.

*We are indebted to Dr. Sam Solomon for permission to use Case No. 7.

action was regular; the rate was 72. The blood pressure was 145/86 mm. Hg. There were no signs of congestion. On fluoroscopy the heart appeared to be slightly enlarged in the anterior view, and its left contour was straight. The right border of the cardiac silhouette exceeded the right sternal margin by a few millimeters. An electrocardiogram revealed left axis deviation and inversion of T in Leads CF_1 through CF_4.

When the patient was re-examined two years later, his condition was unchanged. His capacity for effort was not reduced. Occasionally he complained of "heaviness" in the precordial region, and sometimes he felt pinching in his left arm. An electrocardiogram (Fig. 1) showed inverted T waves in Leads V_1 through V_3. The unipolar limb leads indicated intermediate position of the heart.

CASE 2.—H. D., a 44-year-old man, was examined on June 15, 1948. He complained of fatigue and occasional mild pain in the precordial region which was never associated with effort. He was able to walk for miles and to climb stairs without experiencing discomfort.

On physical examination, the patient presented a deep depression in the region of the lower half of the sternum. The external anteroposterior diameter of the chest at the level of the deepest depression measured 13.5 cm. The lungs were clear. The apex beat of the heart was not palpable with the patient in the supine position. With the patient in the upright posture, the apical thrust was felt in the sixth intercostal space, slightly outside of the left anterior axillary line. No murmurs were heard. The heart action was regular; its rate was 68. The blood pressure was 160/80 mm. Hg. On fluoroscopy the heart appeared to be moderately enlarged to the left in the anterior view. At the right side the cardiac silhouette extended about 2.5 cm. beyond the sternum. An electrocardiogram (Fig. 2) showed inverted T waves in Leads V_1 through V_3. The amplitude of

the inverted T waves decreased gradually from the right side to the left. The unipolar limb leads indicated a vertical position of the heart.

CASE 3.—H. B., a 48-year-old woman, had a history of two partial thyroidectomies which were done twenty and ten years before, respectively. She was admitted to the hospital on May 5, 1948, because of nodular changes in the breast. She complained of fatigue, palpitation, and loss of weight. Her effort capacity had "always" been poor.

On physical examination, a deep depression of the sternum was observed. The external anteroposterior diameter of the chest at the level of the deepest depression measured only 10 cm.

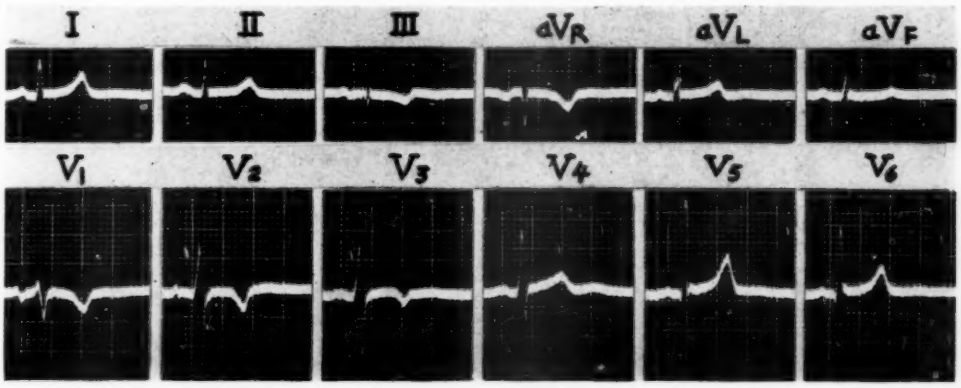

Fig. 1.—Case 1. Inverted T waves are present in Leads V_1 through V_3. The unipolar limb leads indicate intermediate position of the heart.

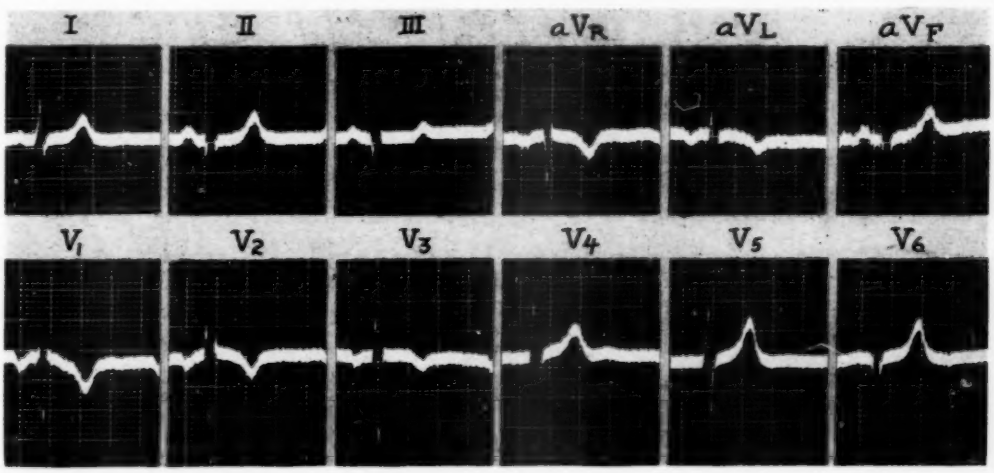

Fig. 2.—Case 2. Inverted T waves are present in Leads V_1 through V_3. The unipolar limb leads indicate vertical position of the heart.

The shortest distance between the posterior aspect of the sternum and the anterior surface of the vertebrae was 0.5 cm., as determined by roentgenologic examination in the lateral view. The lungs were clear. The apex beat of the heart was displaced as far to the left as the posterior axillary line. A systolic murmur was heard in the left second interspace. The heart action was regular; its rate was 94. The blood pressure was 115/75 mm. Hg. Fluoroscopy showed that the heart was not enlarged but was displaced into the left hemithorax. The cardiac silhouette appeared

to be elongated, and the diaphragm was low. The right contour of the heart barely overlapped the left margin of the sternum.

The electrocardiogram (Fig. 3) showed right axis deviation, inversion of T_1 and low diphasic P waves in Lead I; these features resembled those observed with dextrocardia. The unipolar limb leads, however, indicated only vertical position of the heart. The two arm leads presented mainly cavity potential. Because of the marked dislocation of the heart to the left, the cardiac base was closer to the left arm than to the right. For this reason the negative deflections of P, QRS, and T showed greater amplitudes in Lead aV_L than in aV_R. This relationship in the size of the deflections was responsible for the peculiar features of Lead I. In the Leads V_1 through V_4, QRS was of low voltage, its main deflection was directed downward, and the T waves were inverted. Leads V_5 and V_6 presented rS patterns, probably because of marked clockwise rotation of the heart on its longitudinal axis. Lead V_1, which was taken from a point located to the right of the heart, showed mainly inverted deflections of low voltage such as are usually obtained from points in the right midclavicular line when the heart is in normal position and is not enlarged. Lead V_2 resembled Lead V_1.

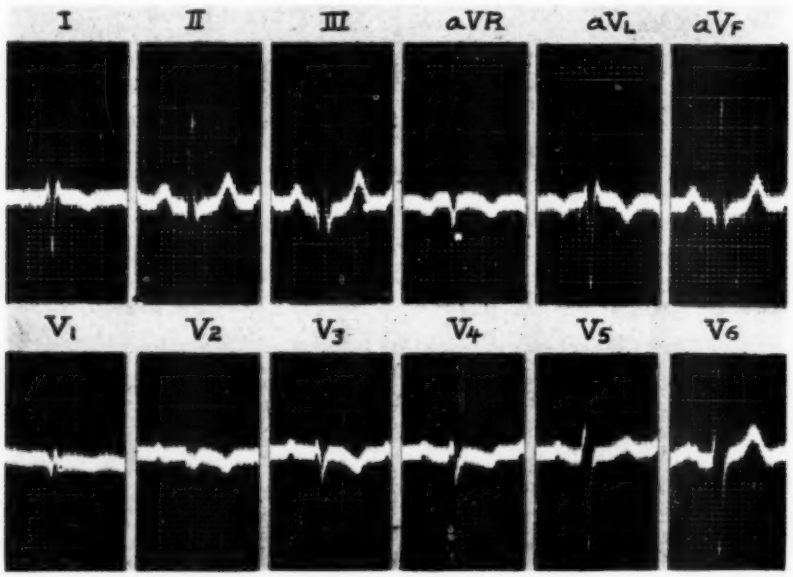

Fig. 3.—Case 3. The unipolar limb leads indicate vertical position of the heart. In Lead aV_L the P and T waves as well as the main QRS deflection are directed downward and are of larger amplitude than in Lead aV_R. Lead I shows deep S deflections associated with diphasic P waves and inverted T waves. In Leads V_1 through V_4 the T waves are inverted and the QRS deflections are of low voltage. Leads V_5 and V_6 present the right ventricular pattern. (From Dressler, William, and Roesler, Hugo, Atlas of Electrocardiography, Springfield, Ill., 1949, courtesy of Charles C Thomas, publisher.)

DISCUSSION

Thirteen patients with funnel chest who presented no significant manifestations of cardiovascular disease were studied. Their electrocardiographic features and thoracic measurements are summarized in Table I. Vertical position of the heart, as indicated by the unipolar limb leads, was present in five instances, horizontal or semihorizontal position in three instances, and intermediate position in four instances. In one patient (Case 4), where unipolar leads were not available, the standard leads indicated left axis deviation.

The most striking electrocardiographic feature was inversion or notching* of T in the chest leads from right precordial positions. This was observed in the precordial leads from positions C_1 to C_3 in six instances, from positions C_1 to C_4 in three instances, and from positions C_1 to C_6 in one instance. Inversion of T was invariably associated with the right ventricular pattern (rS). In one instance (Case 9) the T waves were inverted in Lead V_1 and upright, but unusually low, in Leads V_2 and V_3. Inversion of T in multiple precordial leads was present in ten of the thirteen patients with funnel chest (77 per cent) and was not accounted for by associated pathologic conditions. Enlargement of the cardiac silhouette in the anterior view was present in most of our patients. This is produced by flattening of the heart in the presence of funnel chest rather than by an increase of the cardiac volume.[4,8] Two of the patients who presented inverted T waves in multiple precordial leads were of juvenile age, in which group inversion of the T deflection is a physiological variation. After exclusion of these cases, the incidence of inverted T waves in multiple precordial leads in the group under investigation, which included only white persons, was 60 per cent. In contrast, Littmann[9] observed the "juvenile pattern" of inverted precordial T waves only in 0.5 per cent of a group of 200 healthy white adults. Deeds and Barnes,[10] in a series of 100 healthy adults, noted inversion of T in Lead CF_2 in one instance. According to Johnston, Rosenbaum, and Wilson,[11] inversion of T may occasionally be observed in Lead V_1 but not in the other unipolar precordial leads.

The changes of the T deflection in multiple precordial leads, which were present in a high percentage of our patients with funnel chest, resemble the "juvenile pattern" that is found in close to 60 per cent of healthy children.[14] They are also similar to the pattern of right ventricular "strain" which is observed, for instance, after extensive pulmonary embolism. In neither of these conditions is the cause of inversion of the T deflection in the precordial leads well understood.

Ischemia, secondary to occlusion or narrowing of a coronary artery, causes inversion of the T deflection in direct leads from the affected areas of the myocardium.[12] Pressure exerted upon the heart by the thoracic cage might conceivably have a similar effect. Among the factors responsible for the "juvenile pattern," the difference in the relationship of the heart to the anterior chest wall in children and in adults has been repeatedly stressed.[13,14] In the child the diaphragm is high and the heart is in the horizontal position. Its anterior wall, notably the right ventricle, is in closer contact with the thoracic wall than is the case in adults. Inverted T waves are more frequent in children with thin chest walls and narrow thoracic cages.[14] The varying findings of upright and inverted T waves in the apical chest leads of healthy children were explained by variations in the occurrence of "adult" and "puerile" types of chests in children.[14] In Negroes, who frequently maintain a juvenile chest configuration in adult age, persistence of the "juvenile pattern" of the precordial electrocardiogram is much more frequent than in white adults.[9]

*Notching of T is essentially equivalent to inversion of T.[7]

Patients with funnel chest are often tall, flat-chested individuals of asthenic body build. Moreover, the heart is compressed "like a pancake" by the deformity of the chest.[1,3,4,15,16] Occasionally, a deep groove or indentation at the anterior wall of the heart results from the pressure of the funnel.[6,17,18] It is the right side of the heart that is directly exposed to pressure, whereas the left ventricle facing laterad and dorsad is surrounded by cushioning lung tissue. In our group of patients inversion of T was exclusively observed in precordial leads representing the right ventricular pattern. Similar changes of the electrocardiogram were noted occasionally in healthy adults with flat chests in the absence of funnel deformity. In a case of deep funnel chest, Teplick and Drake[2] observed runs of ventricular tachycardia which they attributed to the presence of an irritable focus in the right ventricle, resulting from the pressure of the depressed sternum.

Inversion of T in precordial leads is in some instances a variable phenomenon. At times inverted T waves may change to flat or upright deflections. It is difficult to say in which way the thoracic deformity produces the electrocardiographic abnormalities. Pressure on the right ventricle may be a factor. Changes in the position of the heart, which permit cavity potential to be transmitted to a wider area of the precordium, must also be considered.

One of our patients (Case 3), who presented an unusually deep funnel chest, showed in the electrocardiogram, in addition to inverted T waves in multiple precordial leads, unusual features in Lead I which resembled changes associated with dextrocardia (Fig. 3). The deep excavation of the sternum approached the vertebrae to a distance of 5 mm. The heart was, as a whole, displaced into the left hemithorax and was in vertical position. Its base, facing both shoulders, was closer to the left than to the right arm. Cavity potential was obviously referred to both arms, but the downward directed deflections of P, QRS, and T were of greater amplitude in the left arm lead than in the right arm lead. Therefore, inverted T waves and diphasic P deflections appeared, together with deep S waves in Lead I.

The electrocardiographic changes which may occur in patients with funnel chest might readily lead to erroneous diagnoses, especially when there are complaints of precordial pain and when the physician reports on tracings without having the benefit of information on clinical data.

SUMMARY

Thirteen patients with funnel chest were studied. In eight adults (60 per cent) the electrocardiogram showed inversion or notching of the T deflection in multiple precordial leads in association with the right ventricular pattern. In one instance where an unusually deep depression of the sternum caused marked dislocation of the heart to the left, the electrocardiogram in Lead I showed features similar to those associated with dextrocardia.

In patients with funnel chest who often complain of precordial pain, inversion of T in right-side precordial leads should not be mistaken for a sign of coronary artery disease. Reading electrocardiograms without knowledge of the chest configuration of the patient might lead to erroneous interpretation.

REFERENCES

1. Master, A. M., and Stone, J.: The Heart in Funnel-shaped and Flat Chests, Am. J. M. Sc. **217**:392, 1949.
2. Teplick, J. G., and Drake, E. H.: The Roentgen and Cardiac Manifestation of Funnel Chest, Am. J. Roentgenol. **56**:721, 1946.
3. Sweet, R. H.: Pectus Excavatum, Ann. Surg. **119**:922, 1944.
4. Evans, W.: The Heart in Sternal Depression, Brit. Heart J. **8**:162, 1946.
5. Grieshaber, H.: Das Herz bei Trichterbrust, Helvet. med. acta. **4**:462, 1937.
6. Hutcheson, J. M.: The Cardiac Complications of Funnel Breast, South. Med. & Surg. **101**:266, 1939.
7. Dressler, W., and Roesler, H.: The Significance of Notched T Waves. Unpublished observations.
8. Rösler, H.: Zur röntgenologischen Beurteilung des Herzgefässbildes bei Thoraxdeformitäten, Arch. klin. Med. **164**:365, 1929.
9. Littmann, D.: Persistence of the Juvenile Pattern in the Precordial Leads of Healthy Adult Negroes, With Report of Electrocardiographic Survey of Three Hundred Negro and Two Hundred White Subjects, Am. Heart J. **32**:370, 1946.
10. Deeds, D., and Barnes, A. R.: The Characteristics of the Chest Lead Electrocardiogram in 100 Normal Adults, Am. Heart J. **20**:261, 1940.
11. Johnston, F. D., Rosenbaum, F. F., and Wilson, F. N.: The Ventricular Complex in Multiple Precordial Leads, Modern Concepts of Cardiovascular Disease, The American Heart Association **112**: No. 6, 1943.
12. Bayley, R. H., and LaDue, J. S.: Electrocardiographic Changes of Impending Infarction, and the Ischemia—Injury Pattern Produced in the Dog by Total and Subtotal Occlusion of a Coronary Artery, Am. Heart J. **28**:54, 1949.
13. Battro, A., and Mendy, T. C.: Precordial Leads in Children, Arch. Int. Med. **78**:31, 1946.
14. Robinow, M., Katz, L. N., and Bohning, A.: The Appearance of the T Wave in Lead IV in Normal Children and in Children With Rheumatic Heart Disease, With Some Observations Concerning the Cause of the T Waves Obtained, Am. Heart J. **12**:88, 1936.
15. Brown, L.: Pectus Excavatum, J. Thoracic Surg. **9**:164, 1939.
16. Kuhns, J. G.: Funnel Chest Deformity, New England J. Med. **204**:1077, 1931.
17. Versé, M.: Uber die kongenitale Trichterbrust mit besonderer Berücksichtigung der normalanatomischen Verhältnisse, Beitr. z. path. Anat. u. z. allg. Path. **48**:311, 1910.
18. Bien, G.: Zur Anatomie und Ätiologie der Trichterbrust, Beitr. z. path. Anat. u. z. allg. Path. **52**:567, 1912.

ATRIAL FLUTTER

I. Clinical Aspects

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WITHIN recent years, the classical concepts of both the nature and treatment of atrial flutter have undergone critical evaluation. Lewis[1] explained the disorder as a single and continuous wave circulating around the combined mouths of the superior and inferior venae cavae, pursuing its own wake and retracing the same path. The intimate association of atrial flutter with atrial tachycardia and atrial fibrillation in occasional patients[2,3] has tended to suggest a similar mechanism in all three. Ashman and Hull[4] believed that in many instances a circus mechanism passing through the sinoatrial or atrioventricular node was present in atrial tachycardia. Barker and associates[5] also thought that paroxysmal atrial tachycardia, particularly in patients with atrioventricular block or alternation of P-P cycle length, could be explained by a circus mechanism. However, investigations in our laboratory, which made use of momentary atrial axes,[6] failed to support the theory of the circus mechanism in atrial tachycardia, and it was concluded that an ectopic site of impulse was more probable.

Experimental studies by Scherf and co-workers[7] and by Prinzmetal and co-workers[8] have given strong support to the Viennese school of cardiologists, who preferred the concept of atrial flutter and fibrillation being produced by one or more rapidly discharging ectopic or parasystolic foci. The observations were made mainly in experimental animals, but they have been apparently confirmed in man by using esophageal leads and the cathode ray oscillograph.

Atrial flutter may be suspected on clinical grounds whenever there is a rapid regular tachycardia with a ventricular rate between 140 and 180 per minute, which shows a transient halving of the ventricular rate either spontaneously or on vagal stimulation. Flutter waves can occasionally be detected in the jugular pulse. Harvey and Levine[9] have observed that frequently the minute changes in the P-R interval in atrial flutter result in a varying intensity of the first sound. However, we have noted a halving of the ventricular rate in many patients with paroxysmal atrial tachycardia.[6a] Whenever atrial flutter exists with a varying atrioventricular block, the mechanism cannot be easily distinguished by clinical means from tachycardia with varying atrioventricular conduction or from atrial fibrillation, although the jugular pulse may be of aid in the latter. For accurate diagnosis, the presence of the rhythm disorder must be confirmed by electrocardiographic studies.

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The electrocardiographic diagnosis of atrial flutter depends on the visualization of regular, continuously undulating c-waves in one or more leads. The criteria demand the demonstration of constant atrial activity, as manifested by the absence of any isoelectric period measuring 0.04 or more second. There is usually an atrial rate of 280 to 360 per minute, as contrasted to atrial rates of 160 to 240 per minute in paroxysmal atrial tachycardia. The characteristic configuration may not appear in Lead I, because the main portion of the atrial impulse propagation is at right angles to the line between the right arm and left arm. It is usually better visualized in Leads II and III. Occasionally, leads over the atria in the 2nd or 3rd left or right interspaces or esophageal leads may be required to show the form considered to be evidence of constant atrial activity.[10] In atrial flutter with 1:1 conduction, the visualization of the flutter waves may be difficult, particularly if there is a concomitant bundle branch block. In such cases, carotid sinus pressure will usually increase the degree of atrioventricular block so that a definite diagnosis may be made.

At times, tracings show a pattern between atrial flutter and atrial fibrillation with the undulating waves more prominent and slower than fibrillation waves, but more rapid and more irregular than flutter waves, and perhaps with transient periods of atrial fibrillation. These have been termed impure flutter or flutter-fibrillation, but appear more closely related to atrial fibrillation in clinical behavior and response than to atrial flutter.

THE PRESENT STUDY

We have reviewed the records of ninety-three episodes of atrial flutter in eighty-two patients treated at the University of Texas in the past twenty-two years. Only patients with pure atrial flutter were considered in the present study; patients with flutter-fibrillation were discarded from the series. Seven of the patients were previously reported by Schwab.[11] We have tabulated the age and sex incidence of atrial flutter and its incidence in various types of heart disease. It also seemed desirable to investigate the symptoms and clinical findings related to the disorder and to study the precipitating, perpetuating, and interrupting factors.

Atrial flutter occasionally occurs as an arrhythmia of short duration, which tends to recur and may in such cases often terminate spontaneously. This contrasts with other cases, in which the arrhythmia may persist for long periods.[12,13] Since the response of these two types to therapy may be different, the patients were divided according to the duration of the arrhythmia. Atrial flutter was considered of short duration when lasting under seventy-two hours; thirty-two patients fell into this classification. It was regarded as established when it had failed to revert within seventy-two hours; fifty patients were in this category.

Table I summarizes the age and sex incidence of atrial flutter in eighty-two patients. The highest incidence was in the sixth and seventh decades. Eighty-three per cent of the patients were over 40 years of age, a proportion higher than that previously reported by Parkinson and Bedford.[14] Men predominated in a ratio of 4.7 to 1.

TABLE I. AGE AND SEX INCIDENCE IN EIGHTY-TWO PATIENTS WITH ATRIAL FLUTTER

AGE	MALE	FEMALE
10 to 19	0	1
20 to 29	1	2
30 to 39	8	2
40 to 49	7	2
50 to 59	17	1
60 to 69	23	5
70 to 79	11	1
80 to 89	1	0
Total	68	14

The underlying organic pathologic condition is listed in Table II with patients divided into those with transient and established flutter. The incidence of rheumatic heart disease in this series, which was only 9.8 per cent, was considerably lower than the 19.3 per cent and 26.9 per cent of previous observers.[14,15] However, a decreased incidence of rheumatic heart disease has been noted on the Gulf Coast[16] and may be responsible for the age incidence of atrial flutter in our study. Arteriosclerosis was a common finding, and in twelve instances atrial flutter complicated acute myocardial infarction. Atrial flutter is an infrequent complication of hyperthyroidism and occurred in only seventeen of 830 patients collected by Parkinson and Bedford.[14] Hyperthyroidism was present in four of our patients with atrial flutter. Seven patients had no clinical or laboratory evidence of organic heart disease. However, four of these had the episodes of atrial flutter related to definite precipitating causes. Levine[17] has pointed out that atrial flutter occasionally occurs in apparently normal hearts, but it is less common than atrial fibrillation in such patients. The one patient with a congenital lesion had a hypoplastic aorta with patent ductus arteriosus.

TABLE II. TYPES OF UNDERLYING HEART DISEASE

HEART DISEASE	ESTABLISHED	TRANSIENT	TOTAL
Arteriosclerotic	14	11	25
Acute myocardial infarction	7	5	12
Arteriosclerotic and hypertensive	8	6	14
Hypertensive	2	1	3
Rheumatic	8	0	8
Syphilitic	3	1	4
Thyrotoxic	3	1	4
Disseminated neoplasia	1	2	3
Congenital	0	1	1
Constrictive pericarditis	1	0	1
No organic heart disease	3	4	7
Total	50	32	82

Precipitating Factors.—Definite precipitating factors other than myocardial infarction are listed in Table III. They were not uncommon in the transient

type, being noted in twelve patients. They were somewhat less frequent in the established type. Five episodes occurred due to digitalis intoxication, and four of these lasted over seventy-two hours. These patients reverted to normal rhythm following withdrawal of digitalis; some had the additional institution of quinidine therapy. Three episodes were encountered when quinidine was given in an attempt to convert atrial fibrillation to sinus rhythm, and in these atrial fibrillation recurred following cessation of quinidine. Although digitalis usually tends to perpetuate atrial fibrillation, in two of our patients atrial flutter developed after digitalization in atrial fibrillation. Trauma and surgical procedures occasionally precipitated the arrhythmia. Ingestion of alcohol to toxicity, diabetic acidosis, and administration of epinephrine were also noted to be associated with the onset of atrial flutter. In five patients the atrial flutter was terminal, due to uremia or disseminated neoplasia.

TABLE III. PRECIPITATING FACTORS IN ATRIAL FLUTTER

	ESTABLISHED (50)	TRANSIENT (32)
Digitalis intoxication	4	1
Quinidine therapy in atrial fibrillation	1	2
Digitalis therapy in atrial fibrillation	0	2
Fracture of femur	0	2
Postpneumonectomy	1	1
Postlaparotomy	1	1
Thyroidectomy	1	0
Cerebral trauma	0	1
Tooth extraction	1	0
Acute alcoholism	1	1
Diabetic acidosis	0	1
Adrenalin and ephedrine (asthma)	1	0
Heavy seafood meal	1	0
Total	12	12

Symptoms.—Parkinson and Bedford[14] found heart failure to exist in twenty-four of fifty-two patients with atrial flutter. It was present in one-third of the patients reported by Bell and Strong.[15] In twenty-three of our patients, the onset of atrial flutter increased the degree of pre-existing congestive heart failure. In ten others the symptoms of left ventricular failure with signs of pulmonary congestion could be related to the onset of the disorder. Two of these patients had suffered a recent myocardial infarction. Five additional patients had marked orthopnea during the episode. Five patients were in a state of peripheral collapse with sweating, rapid ventricular rate, pallor, and fall of blood pressure. Three of these five had atrial flutter with rapid ventricular rate due to 1:1 conduction. Excluding the patients with myocardial infarction, anginal pain occurred in four other patients. One of these had pain referred to the epigastrium, while the remainder complained of precordial pain. Palpitation, weakness, and dyspnea were frequent. Cerebral symptoms occurring during a rapid heart rate are well known.[18]

Embolism is rare after the conversion of atrial flutter to normal rhythm. Although nine of the patients of Parkinson and Bedford[14] had embolic phenomena,

none under observation were in atrial flutter at the time of embolism. It remains as a possible complication in long duration flutter, but it is apparently less likely than in atrial fibrillation.[19] Bellet[20] described embolism as occurring in about 7 per cent of the patients with atrial flutter.

Embolism was observed in only two of our flutter patients. One, a 35-year-old Negro man, had a cerebral embolus after conversion of atrial flutter to sinus rhythm. Another, a 70-year-old white woman, died of thrombosis of the aorta following a saddle embolism at the time of conversion.

Recurrences and Associated Disturbances.—Eight patients had more than one episode of atrial flutter; one patient had five attacks. The longest proved continuous duration of atrial flutter in this series was eleven months. This patient was a 44-year-old man with mitral stenosis, who was finally converted to sinus rhythm with oral quinidine. However, two months later, atrial flutter recurred and was then converted to atrial fibrillation with digitalis.

One patient had atrial flutter with complete atrioventricular block, following an acute myocardial infarction. This patient was moribund and died before any specific medication could be given. This association of atrial flutter with complete atrioventricular block is rare. Askey[21] recently collected thirty-six such cases and added one of his own. Two of our patients had right bundle branch block, which persisted after reversion to sinus rhythm. Two others had delayed intraventricular conduction with block localized in the left ventricle. One patient with digitalis toxicity had episodes of paroxysmal ventricular tachycardia and paroxysmal atrial tachycardia, alternating with the atrial flutter. Two cases of established atrial flutter and three of the short duration type were associated with paroxysmal atrial tachycardia. No instances of the Wolff-Parkinson-White syndrome were encountered.

The recent advances toward establishing atrial flutter as arising from a single ectopic focus[8] made it desirable to ascertain the directions of the flutter waves. It should thus be possible to determine roughly the location of the ectopic focus in the same manner as it is done in ectopic atrial tachycardias. However, the auricular T wave in atrial flutter is prominent, and recognition of the P wave may be difficult. Of the ninety-three episodes of atrial flutter, the direction of the flutter waves was indeterminate in 11 (11.8 per cent). A low atrial focus was probable in sixty-nine patients (74.2 per cent), in which the P waves were negative in Leads II and III. In these sixty-nine patients, P_1 was positive in fifty-eight, flat in six, polyphasic in two, and negative in three. The ectopic focus was considered to be high atrial in the six patients (6.4 per cent) in whom P_2 and P_3 were positive. P_1 was flat in two of these and low positive in four. In the five remaining patients P_1 and P_2 were positive, and P_3 was negative in three and diphasic in two.

The atrial rate varied from 210 to 374 per minute. In addition to the five instances of 1:1 atrioventricular conduction, in forty-six episodes the ventricular rhythm was regular due to a regular atrioventricular block from 2:1 to 4:1. In the other episodes, the atrioventricular block varied from cycle to cycle to produce an irregularity of the ventricular rhythm.

SUMMARY

1. The controversial aspects regarding atrial flutter are discussed with the clinical and electrocardiographic criteria for diagnosis.

2. A study is made of eighty-two patients with atrial flutter, 83 per cent of the patients being over 40 years of age and men predominating in a ratio of 4.7 to 1.

3. Most of the patients had arteriosclerotic heart disease, and in twelve instances atrial flutter complicated myocardial infarction. The incidence of rheumatic heart disease was 9.8 per cent and of thyrotoxicosis 4.9 per cent. Seven (8.5 per cent) had no demonstrable evidence of organic heart disease.

4. In twenty-three patients (28.0 per cent) cardiac decompensation was aggravated by the rapid disorder, and in ten others (12.2 per cent) left ventricular failure was precipitated by atrial flutter. Five patients (6.1 per cent) were in peripheral vascular collapse. Four patients had anginal pain accompanying the rapid heart action. Weakness and cerebral symptoms were occasionally present. Embolism occurred in only two patients with atrial flutter.

5. Since duration of atrial flutter apparently is related to the clinical response, an arbitrary division of seventy-two hours was made between transient and established flutter. Precipitating factors were not uncommon, especially in the short duration flutter.

REFERENCES

1. Lewis, Thomas: Clinical Disorders of the Heart Beat, London, 1920, Shaw & Sons, Ltd., p. 76.
2. Decherd, G. M., and Herrmann, G. R.: The Association of Paroxysmal Atrial Tachycardia With Atrial Flutter or Fibrillation, Am. Heart J. **28**:2, 1944.
3. Evans, William: The Unity of Paroxysmal Tachycardia and Auricular Flutter, Brit. Heart J. **6**:221, 1944.
4. Ashman, R., and Hull, E.: Essentials of Electrocardiography, ed. 2, New York, 1945, The Macmillan Company, p. 219.
5. Barker, P. S., Wilson, F. N., and Johnston, F. D.: The Mechanism of Auricular Paroxysmal Tachycardia, Am. Heart J. **26**:435, 1943.
6a. Decherd, G. M., Herrmann, G. R., and Schwab, E. H.: Paroxysmal Supraventricular Tachycardia With A-V Block, Am. Heart J. **26**:446, 1943.
6b. Decherd, G. M., Ruskin, A., and Herrmann, G. R.: Momentary Atrial Electrical Axes: II. Atrial Flutter, Atrial Fibrillation, and Paroxysmal Tachycardia, Am. Heart J. **29**:20, 1945.
7. Scherf, D., Romano, F. J., and Terranova, R.: Experimental Studies on Auricular Flutter and Auricular Fibrillation, Am. Heart J. **36**:241, 1948.
8. Prinzmetal, M., Corday, E., Brill, I. C., Sellers, A. L., Oblath, R. W., Flieg, W. A., and Kruger, H. E.: Mechanism of the Auricular Arrhythmias, Circulation **1**:241, 1950.
9. Harvey, W. P., and Levine, S. A.: The Changing Intensity of the First Sound in Auricular Flutter; An Aid to the Diagnosis by Auscultation, Am. Heart J. **35**:924, 1948.
10. Ellis, L. B., Lann, L. W., and Faulkner, J. M.: The Value of a Special Auricular Lead and of Carotid-Sinus Pressure in the Electrocardiographic Diagnosis of Tachycardias and Other Disorders of the Heart Beat, New England J. Med. **238**:434, 1948.
11. Schwab, E. H.: Auricular Flutter, Texas State J. Med. **27**:567, 1931.
12. Sprague, H. B., and White, P. D.: Auricular Flutter: Report of a Case of Five Years' Duration With Spontaneous Restoration of Normal Rhythm, J. A. M. A. **90**:1772, 1928.
13. Kossmann, C. E., and Berger, A. R.: Auricular Flutter of Eleven Years' Duration With Observations on Esophageal Electrocardiograms, Ann. Int. Med. **15**:128, 1941.
14. Parkinson, J., and Bedford, D. E.: The Course and Treatment of Auricular Flutter, Quart. J. Med. **21**:21, 1927.

15. Bell, W. N., and Strong, G. F.: Auricular Flutter, Canad. M. A. J. **56**:404, 1947.
16. Decherd, G. M., and Herrmann, G. R.: Rheumatic Heart Disease in Texas, Texas State J. Med. **39**:229, 1943.
17. Friedlander, R. D., and Levine, S. A.: Auricular Fibrillation and Flutter Without Evidence of Organic Heart Disease, New England J. Med. **211**:624, 1934.
18. Barnes, A. R.: Cerebral Manifestations of Paroxysmal Tachycardia, Am. J. M. Sc. **171**:489, 1926.
19. Sodeman, W. A., and Engelhardt, H. T.: The Treatment of Auricular Flutter, Clinics **1**:144, 1942.
20. Bellet, S.: Diagnosis and Treatment of Cardiac Arrhythmias, M. Clin. North America **30**:1307, 1946.
21. Askey, J. M.: Auricular Flutter in Association With Myocardial Infarction; Its Prognosis and Management, Am. J. Med. **6**:453, 1949.

PROGNOSIS IN BUNDLE BRANCH BLOCK

I. Factors Influencing the Survival Period in Right Bundle Branch Block

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FROM the time of the first experimental studies of lesions of the bundle branches by Eppinger and Rothberger,[1] Rothberger and Winterberg,[2] Lewis,[3] and Wilson and Herrmann,[4] the clinical implications of this electrocardiographic finding have been of great interest to physicians. The studies of Wilson and his associates[5] and of others[6] have done much to clarify the terminology, so that there is now general agreement concerning the electrocardiographic patterns of right and left bundle branch block.

A review of the literature reveals a lack of unanimity of opinion in regard to the prognostic significance of this abnormality. Different observers using different criteria and dissimilar methods of study have ended with figures which show a corresponding dissimilarity. The early studies of Carter,[7] Willius,[8] Herrick and Smith,[9] White and Viko,[10] Hart,[11] Cowan and Bramwell,[12] Talley and Reed,[13] Bach,[14] Campbell and Turkington,[15] Graybiel and Sprague,[16] King,[17] and Kaplan and Katz[18] all included cases in which the QRS intervals were less than 0.12 second and frequently neglected to separate right and left bundle branch block. In all of these series there was a preponderance of the left branch type of block, and almost without exception a pessimistic view of prognosis was expressed.

Graybiel and Sprague,[16] on the basis of a series of 395 patients, stated that "bundle branch block almost invariably indicates serious organic disease; the average duration of life of 223 fatal cases in this series, after discovery of the conduction fault, was one year and two months, but eighty-five other patients are still alive after an average of two years and eleven months. With few exceptions, the patients still living are either seriously limited in their activity or are actually in some stage of cardiac decompensation." This reflects, in general, the opinion of others at that time.

Oppenheimer, Rothschild, and Mann,[19] on the basis of observations on ten patients with right bundle branch block, pointed out that patients with this type

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of electrocardiographic pattern might have a better prognosis than those with the more common type of bundle branch block. The five patients followed by von Deesten and Dolgenos[20] and the more extensive series reported by Wood, Jeffers, and Wolferth[21] confirmed these observations. The latter authors suggested that when definite evidence of heart disease was present the patients seemed to follow the expected clinical course without regard to abnormality of the QRS complex. Perera, Levine, and Erlanger[22] reached essentially the same conclusions in a series of 104 patients with complete right bundle branch block. When these were compared with 60 patients with complete left bundle branch block, the prognosis was found to be definitely better in the former group of patients.

Freund and Sokolov,[23] in an analysis of 210 patients with bundle branch block, found that patients with right bundle branch block had a slightly better outlook than those with left, but their figures were much less favorable than those of Wood and associates[21] and of Perera and associates.[22] The studies of Sampson and Nagle[24] and of Bishop and Carden,[25] although differing in criteria, demonstrated a better prognosis for left branch block than did those of previous investigators.

It is obvious that a variety of factors accounts for the divergent results obtained in these follow-up studies; most important of these are (1) different criteria in selection of the patients, as, for example, inclusion of patients with QRS conduction time of less than 0.12 second, (2) failure to separate right and left bundle branch lesions, (3) dissimilar methods of grouping and presentation of the data, and (4) variation in the taking of electrocardiograms as a routine procedure in the absence of clinical evidence of heart disease. It is our impression that intraventricular block will become an increasingly frequent finding as electrocardiographic tracings become a routine part of a complete examination or of preoperative evaluation of the older patient.

The problem of prognosis in relation to this lesion is twofold: namely, that of the patient with no, or minimal, symptoms of heart disease, and that of the patient with definite clinical evidence of various types of heart disease. Figures on a large number of "normal" individuals for proper evaluation of the former problem are still inadequate. This report will deal for the most part with patients who fall in the latter group.

In the first part of this study we shall deal only with the factors which influence the survival time in right bundle branch block. In a later communication we will analyze the left branch type in a similar fashion and then compare the two electrocardiographic patterns with regard to the above factors as well as to their relative incidence. The indeterminate, intermediate, or incomplete types of bundle branch block will not be considered in this study.

METHOD OF STUDY

The cases analyzed in this study were drawn from the electrocardiographic files of the Cardiac Laboratory of the Massachusetts General Hospital and consisted of those in which the following criteria for right bundle branch block were fulfilled. All patients with a QRS conduction time of 0.12 second or over with

a broad S wave in Lead I were included, except for patients with complete heart block who were discarded when this was present in the first record showing a prolonged QRS interval. Patients with short P-R intervals (Wolff-Parkinson-White syndrome) were not used. Patients in whom the initial data were incomplete and unobtainable (that is, when patients were referred for electrocardiograms by physicians outside the hospital or by insurance companies) were also excluded. Patients were not ruled out because of incomplete follow-up data if the initial data were complete or if the address of the patient or the address of the referring physician could be ascertained.

In all patients in whom multiple precordial leads were available, these were used to confirm or exclude the diagnosis of right bundle branch block. If the case was of the indeterminate or intermediate type and not clearly of the right branch, it was excluded. Our final series consisted of 281 patients in whom the above-outlined criteria were fulfilled. No attempt was made to separate private from ward cases or outpatients from inpatients.

The follow-up study dated from the first time right bundle branch block was diagnosed electrocardiographically; every attempt was made to secure the earliest electrocardiograms if such had been recorded elsewhere. A letter was sent to each patient or, if he had died, to his family or friends. In addition, a letter was sent to the referring physician and to any or all other physicians who had been following, or had knowledge of, the patient. If the patient had been in other hospitals or institutions, additional information was requested of them.

The letter to the patient asked for an evaluation of his cardiac symptoms, if any, and an estimate as to whether they were mild, moderate, or severe; if he were able to work; and if he were limited, whether this was due to a condition other than cardiac disability.

The physician, family, or friends were requested to give essentially the same information: if the patient were dead, to give the date of his death, the mode and cause of death, the events leading up to it, and the post-mortem findings if an autopsy had been performed.

Of the 93 patients still alive at the time this study was completed, those who had not had a follow-up note or electrocardiogram within two years were requested to return if possible for a personal interview, physical examination, and electrocardiogram.

The data collected were analyzed for the total group of 281 patients in regard to relationship of the following factors to survival time: age, sex, etiology of the underlying heart disease, degree of cardiac enlargment, and duration of the QRS conduction time. The cause of death and autopsy findings when known are listed. Because previous studies have shown that patients who survive the first year have a better prognosis than the total group, and because many of the patients in our series had their first electrocardiogram taken after an acute myocardial infarct or when they were in a terminal condition, the group who survived the first year was analyzed separately and compared with the total.

RESULTS

Table I shows the age distribution of the 281 patients with right bundle branch block, the number of male and female patients in each age group, and the

TABLE I. AGE AND SEX DISTRIBUTION OF PATIENTS WITH RIGHT BUNDLE BRANCH BLOCK WITH YEAR OF FOLLOW-UP IF PATIENT IS ALIVE OR YEAR DIED OR LOST FROM SERIES

AGE DISTRIBUTION		YEAR OF FOLLOW-UP 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	TOTAL	MALE	FEMALE
1. 0 to 9.99	Alive	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0		
	Dead	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	1	0
	Lost	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	1		
2. 10 to 19.99	Alive	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0		
	Dead	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0	0
	Lost	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0		
3. 20 to 29.99	Alive	1	—	—	—	—	1	1	—	—	—	1	—	—	—	—	4		
	Dead	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	5	4	1
	Lost	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0		
4. 30 to 39.99	Alive	1	—	—	—	2	—	—	—	1	—	—	—	—	—	—	4		
	Dead	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	3	8	2	6
	Lost	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1		
5. 40 to 49.99	Alive	1	—	—	—	1	1	1	1	—	1	2	—	—	—	—	8		
	Dead	3	4	—	—	—	—	1	—	—	—	—	—	—	1	—	9	36	27	9
	Lost	8	3	1	—	3	—	1	—	—	—	—	—	—	—	3	19		
6. 50 to 59.99	Alive	1	1	1	4	3	2	—	3	2	—	1	—	—	1	—	19		
	Dead	15	3	—	2	1	1	—	2	—	1	—	—	—	—	—	25	76	55	21
	Lost	20	3	—	1	—	2	—	1	1	1	1	—	1	1	—	32		
7. 60 to 69.99	Alive	10	4	1	2	6	4	4	1	1	2	1	—	—	—	—	36		
	Dead	9	3	6	3	—	1	—	1	1	—	—	—	—	—	—	24	81	59	22
	Lost	7	3	3	3	—	1	1	1	—	1	—	—	1	—	—	21		
8. 70 to 79.99	Alive	4	3	3	1	1	3	—	2	—	2	1	—	—	—	—	20		
	Dead	14	2	1	4	—	3	—	—	1	—	—	—	—	—	—	25	62	46	16
	Lost	11	—	4	1	1	—	—	—	—	—	—	—	—	—	—	17		
9. 80 to 89.99	Alive	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—	2		
	Dead	—	4	—	—	—	1	—	—	—	—	—	—	—	—	—	5	11	8	3
	Lost	2	1	1	—	—	—	—	—	—	—	—	—	—	—	—	4		
10. 90 to 99.99 or over	Alive	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0		
	Dead	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	1	1	0
	Lost	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0		
Totals																	281	203	78

year of follow-up during which the patient died or was lost from the series, or the length of time he was followed if he was known to be still alive. The highest incidence of right bundle branch block occurred in the age group of 50 to 80 years inclusive, with men predominating in all groups except from 30 to 40 years inclusive. (The number of patients in this latter group is too small to be significant, however.) At the end of the period of study, 93 patients were known to be alive, 93 more known to be dead, and in 95 the data were incomplete. In the "lost" group 46 were known to have lived longer than 1 year, 1 was lost after 15 years, 1 after 21 years, and 1 at the end of 25 years.

The distribution of the patients alive, dead, and lost from the series during each year of follow-up is shown in Table II. There were 41 patients who had been followed longer than 5 years and who were still alive at the time this study ended, and 14 other patients died after living longer than 5 years. In addition, there were 17 patients who were followed longer than 5 years but were "lost" thereafter; of those it is not known definitely whether they are now alive or dead. This makes a total of 72 patients with right bundle branch block who are known to have lived 5 years or longer. It is of interest to point out that of the patients lost the majority (49) were lost during the first year of follow-up. We have considered all patients as dead at the end of the year of follow-up during which they were lost from the series. Although we realize this may not be true in all cases, it would be statistically unsound to disregard these patients, since the most common reason for not being able to locate a patient is the death of that patient. In analyzing those patients who survived the first year of follow-up separately from the total, the influence of the large number lost during the first year is minimized. It is for this and other reasons pointed out earlier that a more accurate index of survival time is indicated by the group of patients who survived the first year of follow-up.

TABLE II. DISTRIBUTION OF PATIENTS ALIVE, DEAD, AND LOST EACH YEAR OF FOLLOW-UP

YEAR OF FOLLOW-UP	PATIENTS STILL ALIVE	PATIENTS DEAD	PATIENTS LOST
1st	19	45	49
2nd	8	16	10
3rd	5	7	9
4th	8	10	6
5th	12	1	4
6th	12	6	3
7th	6	1	2
8th	7	3	2
9th	4	2	1
10th	5	1	2
11th	6	0	1
12th	0	0	0
13th	0	0	2
14th	1	1	0
15th or over	0	0	4
Total (281)	93	93	95

The average duration of life in years with relation to the age at which the diagnosis of right bundle branch block was established is shown in Table III. The total group is compared with those who survived the first year. These figures confirm the observations of Sampson and Nagle,[24] Bishop and Carden,[25] and others[26] that those patients who survive the first year after the diagnosis of bundle branch block have the best prognosis. The over-all picture presented by our figures is comewhat more optimistic than that given by several of the earlier investigators.

TABLE III. AVERAGE SURVIVAL TIME IN RELATION TO AGE AT WHICH RIGHT BUNDLE BRANCH BLOCK WAS DIAGNOSED

AGE GROUP	TOTAL PATIENTS IN SERIES	PATIENTS WHO SURVIVED ONE YEAR	AVERAGE SURVIVAL TIME IN YEARS	
			OF TOTAL PATIENTS IN SERIES	OF PATIENTS WHO SURVIVED ONE YEAR
0 to 9.9	1	1	15+	15
10 to 19.9	0	0	0	0
20 to 29.9	5	3	5.2	8.0
30 to 39.9	8	4	3.1	5.2
40 to 49.9	36	24	4.9	6.8
50 to 59.9	76	40	3.8	6.3
60 to 69.9	81	55	3.7	5.1
70 to 79.9	62	33	3.0	4.8
80 to 89.9	11	8	2.5	3.1
90 to 99.9	1	0	1.0	0

In Table IV the relationship of the total group to those who survived the first year was compared in regard to sex, to whether the bundle branch block was typical or atypical, and to the degree of cardiac enlargement. The first two factors seemed to have little influence on the over-all outlook except that women had a slightly better outlook than men. The degree of cardiac enlargement seemed to exert a definite influence on the prognosis, in that patients with no cardiac enlargement showed a definitely better outlook than those with marked enlargement of the heart.

The average duration of life in relation to QRS duration is shown in Table V. The reason that patients with QRS conduction times of 0.12 second seemed to have slightly less favorable prognoses than those with QRS intervals of 0.13 and 0.14 second is not clear. Although a large number of the former died or were lost during the first year of follow-up, the difference between the 2 groups is still present in those who survived the first year.

In Table VI the distribution of the various degrees of cardiac enlargement occurring in each group with respect to the QRS duration is shown. It can be seen that a higher percentage of patients with a QRS duration of 0.12 second have markedly enlarged hearts and a lower percentage have normal size hearts than in the group with QRS intervals of 0.13 and 0.14 second. This suggests that the shorter survival times of the former group were associated with more severe

TABLE IV. RELATIONSHIP OF SEX, DIRECTION OF T_1, AND HEART SIZE TO SURVIVAL PERIOD IN RIGHT BUNDLE BRANCH BLOCK

	TOTAL PATIENTS IN SERIES	PATIENTS WHO SURVIVED ONE YEAR	AVERAGE SURVIVAL PERIOD IN YEARS	
			OF TOTAL PATIENTS IN SERIES	OF PATIENTS WHO SURVIVED ONE YEAR
Male	203	116	3.5	5.3
Female	78	50	4.2	6.0
Typical right bundle branch block (upright T_1)	202	119	3.7	5.6
Atypical right bundle branch block (inverted T_1)	79	47	3.6	5.3
No cardiac enlargement	127	79	4.2	6.2
Slight cardiac enlargement	78	49	3.6	5.1
Moderate cardiac enlargement	34	20	3.3	4.9
Marked cardiac enlargement	42	18	2.4	4.3

TABLE V.

QRS DURATION IN SECONDS	TOTAL PATIENTS IN SERIES	PATIENTS WHO SURVIVED ONE YEAR	AVERAGE SURVIVAL PERIOD IN YEARS	
			OF TOTAL PATIENTS IN SERIES	OF PATIENTS WHO SURVIVED ONE YEAR
0.12	109	62	3.5	5.3
0.13	60	38	3.9	5.7
0.14	63	38	3.8	5.7
0.15	23	12	2.7	5.8
0.16	13	9	2.5	4.7
0.17	7	4	2.4	3.5
0.18	4	2	5.2	9.5
0.19	0	0	0	0
0.20	2	1	4.5	8.0

underlying heart disease. It is also possible that cardiac enlargement, either hypertrophy or dilatation, contributed in part to the prolonged QRS conduction time.

Table VII shows the distribution of the etiological type of heart disease and the average duration of life after the diagnosis of right bundle branch block. Of the 95 patients with a diagnosis of coronary heart disease, 55 had suffered definite myocardial infarction, and 17 of these 55 had the anginal syndrome. The remainder of the 95 patients had no history of definite myocardial infarction, but all manifested the anginal syndrome. In the 99 patients listed under the heading of "undetermined etiology" there was no clear evidence for the etiology of the bundle branch block. One patient had rheumatoid arthritis, 1 patient had Buerger's disease (without clinical evidence of coronary disease), 1 patient had hypothyroidism, 2 patients had hyperthyroidism, 5 patients had cor pulmonale,

and 1 patient had idiopathic myocardial hypertrophy. Of the above 99 patients 57 had either minimal or no cardiac symptoms; however, there is little doubt that many of these patients represent "asymptomatic coronary disease," since the majority were men over 40 years old. It is of interest that their prognosis is significantly better than those patients with clinical symptoms of coronary disease, indicating that the latter had a greater degree of coronary heart disease as shown by its easier recognition. If the average survival time is figured for these 57 patients separately, it is 3.9 years and for the 34 patients who survived the first year of follow-up it is 5.9 years. This is somewhat lower than for the total group, but this may be due to the fact that 3 patients in the total group lived over 15 years. The low average duration of life in the rheumatic group undoubtedly reflects the degree to which rheumatic heart disease must develop before bundle branch block appears. The 2 patients listed as "syphilitic" had no clear evidence of syphilitic heart disease (other than the electrocardiographic finding) beyond positive blood serology, and they did not seem to fall into the other groups.

TABLE VI. DURATION OF QRS INTERVAL WITH RESPECT TO HEART SIZE

QRS DURATION IN SECONDS	SIZE OF THE HEART								TOTAL PATIENTS
	NORMAL		SLIGHTLY ENLARGED		MODERATELY ENLARGED		MARKEDLY ENLARGED		
	NO.	%	NO.	%	NO.	%	NO.	%	
0.12	46	42	29	27	12	11	22	20	109
0.13	31	52	15	25	6	10	8	13	60
0.14	29	46	21	33	9	14	4	7	63
0.15	15	65	4	17	2	9	2	9	23
0.16	4	31	3	23	4	31	2	15	13
0.17	2	29	4	57	1	14			7
0.18	2	50	1	25			1	25	4
0.19									0
0.20							2	100	2

In the group of 93 patients who were known to be dead, autopsies were known to have been performed on but 13; of these, 4 died of myocardial infarction and 6 of congestive heart failure. Of these latter 6 patients, 3 had valvular lesions, 1 aortic stenosis (thought to be calcareous), and 2 rheumatic heart disease. In the remaining 3 patients 1 had chronic cor pulmonale with marked arteriosclerosis of the pulmonary artery, 1 had chronic bronchitis, cor pulmonale, and coronary arteriosclerosis, and the third had extensive coronary arteriosclerosis.

There were 45 patients who were known to have died during the first year of follow-up, of whom 12 died either suddenly or of a definite myocardial infarction and 13 of congestive heart failure. Three deaths were related to the heart disease which was present, and in 17 the cause of death was unknown or was unrelated to the heart.

TABLE VII. SURVIVAL OF PATIENTS WITH RIGHT BUNDLE BRANCH BLOCK IN RELATION TO ETIOLOGY

TYPE OF HEART DISEASE	NUMBER OF PATIENTS LIVING EACH YEAR OF FOLLOW-UP BEFORE DYING OR BEING LOST FROM SERIES															TOTAL PATIENTS IN SERIES	PATIENTS WHO SURVIVED ONE YEAR	AVERAGE SURVIVAL PERIOD IN YEARS	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			OF TOTAL PATIENTS IN SERIES	OF PATIENTS WHO SURVIVED ONE YEAR
Coronary	40	12	5	9	9	6	3	3	0	4	2	0	1	0	1	95	55	3.0	4.5
Hypertensive	23	7	7	4	3	3	1	3	1	2	1	0	0	1	0	56	33	3.4	5.1
Rheumatic	13	5	0	0	1	2	0	1	1	0	0	0	0	0	0	23	10	2.4	4.4
Congenital	3	1	0	0	0	1	1	0	0	0	0	0	0	0	0	6	3	3.0	5.0
Undetermined etiology	36	9	8	10	3	9	4	5	4	2	4	0	1	1	3	99	63	4.3	6.2
Syphilitic (?)	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	2	2	7.0	7.0

DISCUSSION

The most important factor influencing the prognosis in right bundle branch block is the underlying heart disease. This is clearly shown when heart size is used as an indication of the severity of the heart disease, the survival time varying inversely with the degree of cardiac enlargement. The relationships of etiological types of heart disease, where the groups are large enough to be significant, show that right bundle branch block, when associated with clear-cut coronary heart disease or rheumatic heart disease, has a less favorable outlook than when it occurs as a complication of hypertensive heart disease without any pathognomonic evidence of coronary or rheumatic heart disease, but the average survival time is longest of all in the group we have classified as of undetermined etiology. A few of these patients had evidence of heart disease other than the electrocardiographic finding, or they had other diseases which could have increased the cardiac burden, such as thyrotoxicosis, myxedema, or cardiac enlargement of unknown etiology. In 7 of these patients there was a history of diphtheria, but in only 1 was the bundle branch block definitely known to have been present and persistent following that illness. There is at present no available evidence to show that the incidence of bundle branch block later in life is higher in patients who have had diphtheria than in the remainder of the population. The important point in this group of patients, in whom the electrocardiogram is the principal abnormality, is that their outlook may be much better than that of patients with definite clinical evidence of coronary heart disease.

The electrocardiogram showed little that was of prognostic value except that patients with QRS conduction times of 0.12 second or over seemed to have a less favorable outlook than those with a QRS time of intermediate duration (0.13 to 0.14 second). The apparent shorter survival time of those patients with QRS conduction times of 0.12 second, as compared to those with QRS conduction times of 0.13 to 0.14 second, is difficult to explain. It is not due to a difference in the number of patients "lost" in the different groups: 25 per cent of the patients with QRS durations of 0.12 second were lost during the first 4 years of follow-up, while 34 per cent of the group with QRS durations of 0.13 to 0.14 second were lost during the same period. Thus, it is obvious that the patients in the latter group actually lived longer. The higher percentage of patients with cardiac enlargement in the group with QRS duration of 0.12 second indicates that the underlying heart disease was more severe in this group and accounts for the poorer prognosis.

The direction of the T wave in Lead I in relation to the main deflection of the QRS seemed to have no effect on prognosis. This is contrary to the findings of Willius, Dry, and Reeser,[27] but the two groups are not strictly comparable, since the above authors included patients with QRS durations of 0.11 second and figured the life expectancy of right and left branch block together (except that the "S" wave type of right branch block was classified separately). Our results would indicate that in right bundle branch block no prognostic significance can be attached to the direction of the T wave in Lead I or in the classification of the conduction disturbance as typical or atypical, concordant or discordant.

SUMMARY AND CONCLUSIONS

1. The factors influencing the prognosis of right bundle branch block have been analyzed in a series of 281 patients electrocardiographed at the Massachusetts General Hospital. The most important of these is the underlying heart disease, both as to type and to degree. The highest degree of correlation was found to exist between heart size and survival time. Rheumatic and obvious coronary heart disease had the least favorable outlook, while right bundle branch block in the absence of a clear etiological factor (sometimes called "asymptomatic" coronary heart disease, manifested by the electrocardiographic abnormality alone) had the best outlook.

2. There was a preponderance of male patients of almost 3 to 1. Female patients tolerated the lesion somewhat better than male. The mortality was fairly constant between the ages of 50 to 80 years, slightly higher in the 30 to 40 year age group (probably because of the rheumatic patients), and markedly increased after the age of 80 years, as would be expected. The patients who survived the first year of follow-up did better than the total group.

3. Survival for longer than 5 years after the discovery of the right bundle branch block was known in the case of 72 patients who could be followed; of these 72, 17 were dead at the time of this follow-up study, while of the remaining 55, there were 41 still alive, and 14 were lost at various intervals after being followed longer than 5 years. This group of 72 patients makes up 27 per cent of the entire series of 281 patients and 39 per cent of the 186 who could be traced. Death within 1 year was known in the case of 45 patients who could be followed (16 per cent of the total series and 24 per cent of those traced), but it is likely that a considerable number of the 49 patients not traced at the end of the first year died during that year.

4. The prognosis of right bundle branch block is very variable and is dependent on the prognosis of other clinical abnormalities, in particular, angina pectoris and cardiac enlargement. Though per se an indication of some degree of heart disease, it is not infrequently found in persons surviving more than 5 years after its discovery.

REFERENCES

1. Eppinger, H., and Rothberger, C. J.: Ueber die Folgen der Durchneidung der Tawaraschen Schenkel des Reizleitungssystens, Zentralbl. f. klin. Med. **70**:1, 1910.
2. Rothberger, C. J., and Winterberg, H.: Zur Diagnose der einseitigen Blockierung der Reizleitung in den Tawaraschen Schenkel, Zentralbl. f. Herzkrankh. **5**:206, 1913.
3. Lewis, T.: The Spread of the Excitatory Process in the Vertebrate Heart, Phil. Tr., Lond., Series B **207**:221, 1916.
4. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, Heart **8**:229, 1921.
5a. Barker, P. S., Macleod, A. G., Alexander, J., and Wilson, F. N.: The Excitatory Process in the Exposed Human Heart, Tr. A. Am. Physicians **44**:125, 1929.
5b. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle Branch Block, Am. Heart J. **7**:305, 1932.
5c. Wilson, F. N.: Concerning the Form of the QRS Deflections of the Electrocardiogram in Bundle Branch Block, J. Mt. Sinai Hosp. **8**:1110, 1942.
6a. Roberts, G. H., Crawford, J. H., and Abramson, D. I.: Experimental Bundle Branch Block in the Monkey, J. Clin. Investigation **14**:867, 1935.
6b. Battro, A., and Bidoggia, H.: Endocardiac Electrocardiogram Obtained by Heart Catheterization in the Man, Am. Heart J. **33**:604, 1947.

6c. Sodi-Pallares, D., Viscaino, M., Soberón, J., and Cabrera, C. E.: Comparative Study of the Intracavity Potential in Man and in Dog, Am. Heart J. **33**:819, 1947.
6d. Sodi-Pallares, D., Thomsen, P., and Soberón, J.: New Contributions to the Study of the Intracavity Potential in Cases of Right Bundle Branch Block in the Human Heart, Am. Heart J. **36**:1, 1948.
7. Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the Auriculoventricular Bundle, Arch. Int. Med. **13**:803, 1914.
8a. Willius, F. A.: Arborization Block, Arch. Int. Med. **23**:431, 1919.
8b. Willius, F. A.: Clinical Features of Cases Exhibiting Electrocardiograms Conforming to Those of Experimental Complete Bundle Branch Block, Am. Heart J. **1**:576, 1926.
9. Herrick, J. B., and Smith, F. M.: Clinical Observations on Block of the Branches of the Auriculoventricular Bundle, Am. J. M. Sc. **164**:469, 1922.
10. White, P. D., and Viko, L. E.: Clinical Observations on Heart Block, Am. J. M. Sc. **165**:659, 1923.
11. Hart, T. S.: Block of the Branches of the Bundle of His, Arch. Int. Med. **35**:115, 1925.
12. Cowan, J., and Bramwell, J. C.: The Clinical Aspect of Bundle Branch Block, Quart J. Med. **19**:95, 1925.
13. Talley, J. E., and Reed, O. K.: A Study of Twenty-Eight Cases of Bundle Branch Block, Am. Heart J. **1**:257, 1926.
14. Bach, F.: On the Clinical Significance of Right Branch Bundle Block, Quart. J. Med. **23**:261, 1930.
15. Campbell, S. B. B., and Turkington, S. I.: Right Bundle Branch Block, Quart. J. Med. **24**:481, 1930.
16. Graybiel, A., and Sprague, H. B.: Bundle Branch Block; An Analysis of 395 Cases, Am. J. M. Sc. **185**:395, 1933.
17. King, J. T.: Bundle Branch Block: A Case Analysis With Special Reference to Incidence and Prognosis, Am. J. M. Sc. **187**:149, 1934.
18. Kaplan, L. G., and Katz, L. N.: The Prognosis of Intraventricular Block, Am. Heart J. **18**:145, 1939.
19. Oppenheimer, B. S., Rothschild, M. A., and Mann, H.: Cardiographic Differentiation of a Sub-group of Intraventricular Block With Observations on the Prognosis, J. Clin. Investigation **1**:592, 1925.
20. Von Deesten, H. F., and Dolganos, M.: Atypical Bundle Branch Block With a Favorable Prognosis, Am. J. M. Sc. **188**:231, 1934.
21. Wood, F. C., Jeffers, W. A., and Wolferth, C. C.: Follow-up Study of 64 Patients With a Right Bundle Branch Conduction Defect, Am. Heart J. **10**:1056, 1935.
22. Perera, G. A., Levine, S. A., and Erlanger, H.: Prognosis of Right Bundle Branch Block: A Study of 104 Cases, Brit. Heart J. **4**:35, 1942.
23. Freund, H. A., and Sokolov, R.: Bundle Branch Block, Arch. Int. Med. **63**:318, 1939.
24. Sampson, J. J., and Nagle, O. E.: The Prognosis of Bundle Branch Block and Other Intraventricular Conduction System Lesions, Am. J. M. Sc. **191**:88, 1936.
25. Bishop, L. F., Jr., and Carden, G. A., Jr.: The Prognosis of Bundle Branch Block, Am. Heart J. **17**:275, 1939.
26. Gober, O. B., and Sloan, J. Q.: Prognosis of Bundle Branch Block, Texas State J. Med. **45**:82, 1949.
27a. Willius, F. A., Dry, T. J., and Reeser, R., Jr.: Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram. I. General Considerations of Bundle Branch Block With Concordant and With Discordant Graphs and the Wide S Wave Pattern, Based on 1,611 Cases, Arch. Int. Med. **67**:1008, 1941.
27b. Reeser, R., Jr., Willius, F. A., and Dry, T. J.: Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram. II. Special Consideration of Bundle Branch Block With Concordant Graphs and With Discordant Graphs, Arch. Int. Med. **67**:1027, 1941.
27c. Dry, T. J., Willius, F. A., and Reeser, R., Jr.: Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram. III. Special Consideration of the Wide S Wave Pattern, With Report of Three Cases, Arch. Int. Med. **67**:1034, 1941.

THE EFFECT OF ATROPINE ON THE CARDIAC MECHANISM IN ANOMALOUS ATRIOVENTRICULAR CONDUCTION

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THE clinical entity known as the syndrome of "anomalous atrioventricular conduction," or "Wolff-Parkinson-White syndrome," is now widely recognized. The history of the clinical recognition and the development of the modern concepts of the etiology and pharmacology of this syndrome have proved most interesting. The proper clinical evaluation of this syndrome was established by Wolff, Parkinson, and White,[22] who reported a series of eleven cases in 1930 characterized by the following features: (1) electrocardiographic peculiarities consisting of abnormal shortening of the P-R interval with a pronounced increase in the duration of the QRS complex; (2) complete absence of physical signs of organic heart disease; (3) the occurrence of heterotopic paroxysms of tachycardia; and (4) reversion of the anomalous electrocardiographic pattern to a normal one either spontaneously, following exercise, or after the administration of atropine.

This paper will deal with the physiological action of atropine on the cardiac conduction mechanism and its use as a diagnostic aid in six patients showing electrocardiographic patterns characterized by a short P-R interval and a prolonged QRS complex.

PROCEDURE

Six patients were studied in this series. Each patient, having been found nonsensitive to atropine sulfate, was attached to a direct-writing electrocardiograph in a routine fashion. A tracing was taken of the three standard leads, the augmented limb leads of Goldberger, and the six precordial V leads. Then 1/75 to 1/50 gr. of atropine sulfate was rapidly injected into an antecubital vein while a continuous electrocardiographic tracing was being recorded by the direct-writing electrocardiograph. An attempt was made in each patient to secure a tracing showing the change in the conduction mechanism in the above-mentioned leads following the intravenous administration of atropine sulfate.

RESULTS

Case 1.—J. E., a 31-year-old white man, had had episodes of tachycardia accompanied by crushing substernal pain since childhood. He was refused for military service, being told he had

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coronary heart disease following electrocardiographic studies. The patient developed a severe neurocirculatory asthenia and was referred to the cardiac clinic of the Los Angeles County Hospital. Physical examination and fluoroscopy of the heart were entirely normal. The blood pressure was 120/70 mm. Hg. A routine electrocardiogram revealed anomalous atrioventricular conduction.

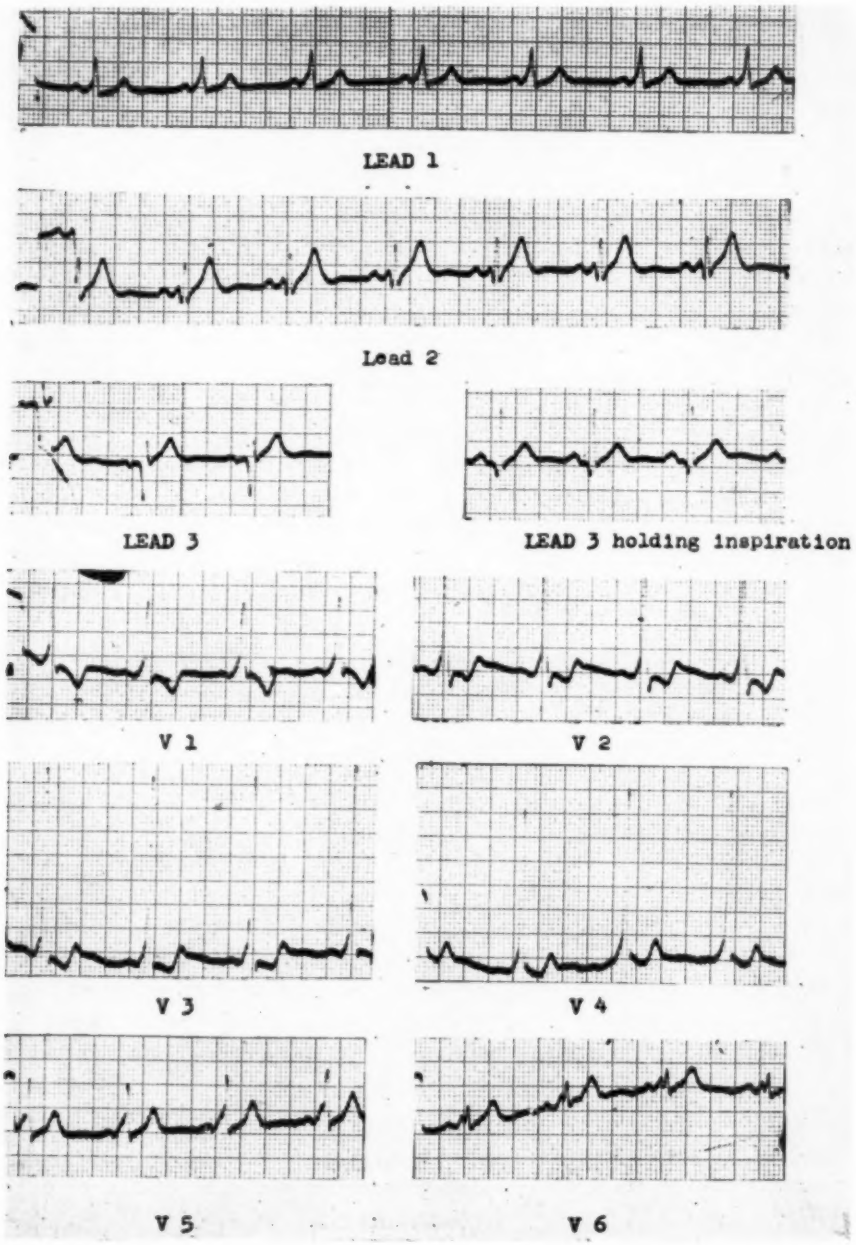

Fig. 1.—Electrocardiogram of J. E. showing anomalous atrioventricular conduction. The P-R interval varies from 0.08 to 0.10 second, and the QRS complex measures up to 0.16 second.

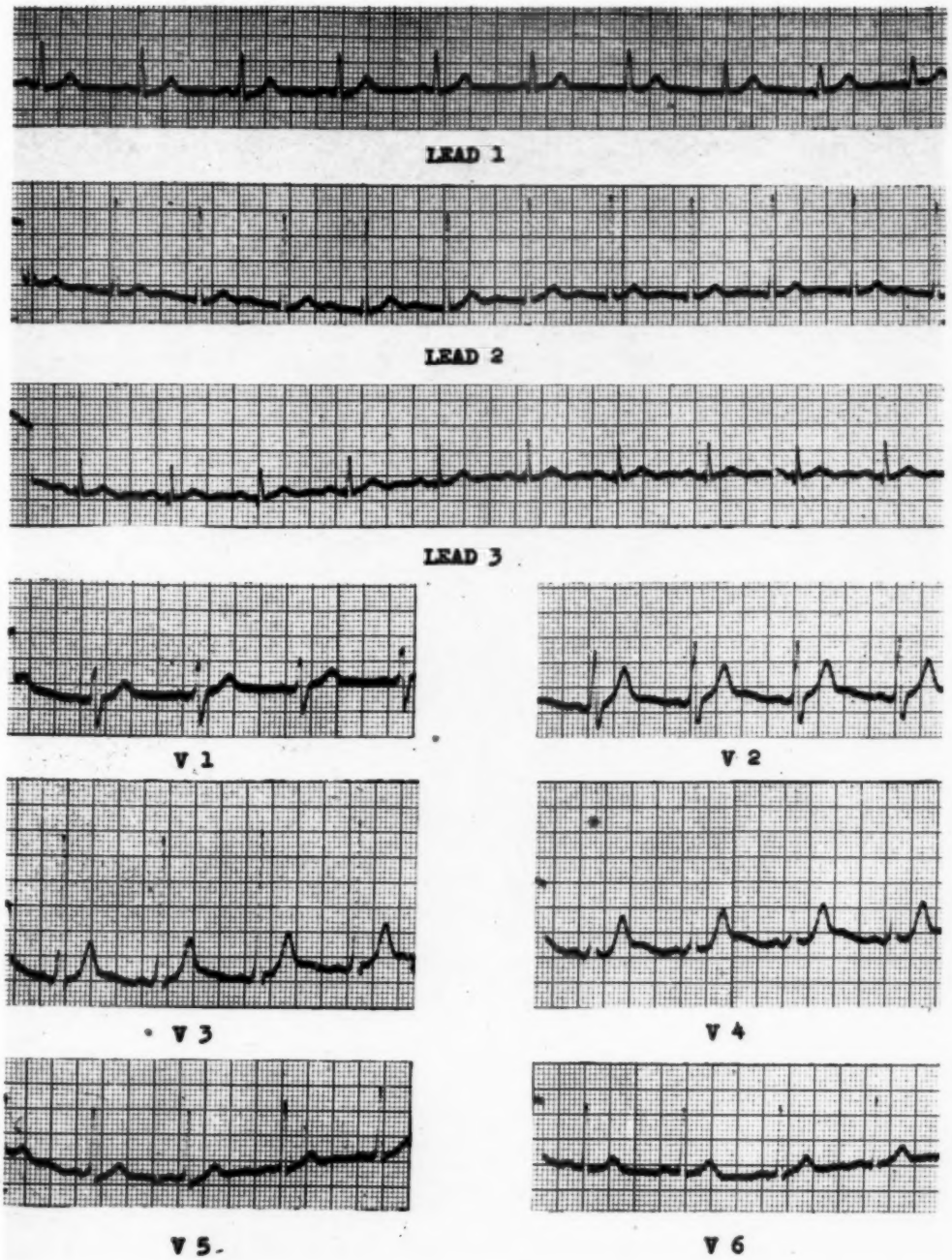

Fig. 2.—Electrocardiogram of J. E. following the intravenous injection of 1/75 gr. of atropine sulfate. In Lead I a normal sinus rhythm is now present with a P-R interval of 0.18 second and a QRS complex of 0.08 second. After the fourth complex, the P-R interval gradually shortens with the appearance of a middle nodal rhythm which persists throughout Lead II. In Lead III a normal sinus rhythm has reappeared which persists throughout most of the remainder of the tracing. Occasional complexes again show anomalous atrioventricular conduction.

Electrocardiographic Studies.—Fig. 1 represents the initial electrocardiogram taken upon admission to the cardiac clinic. It shows anomalous atrioventricular conduction with a P-R interval of 0.08 to 0.10 second and a QRS complex up to 0.16 second in duration. Fig. 2 was taken following the intravenous injection of 1/75 gr. of atropine sulfate. The atropine first produced a normal sinus mechanism, which in turn was followed by a gradually developing middle nodal rhythm as the P-R interval shortened until the P wave was buried in the QRS complex. The

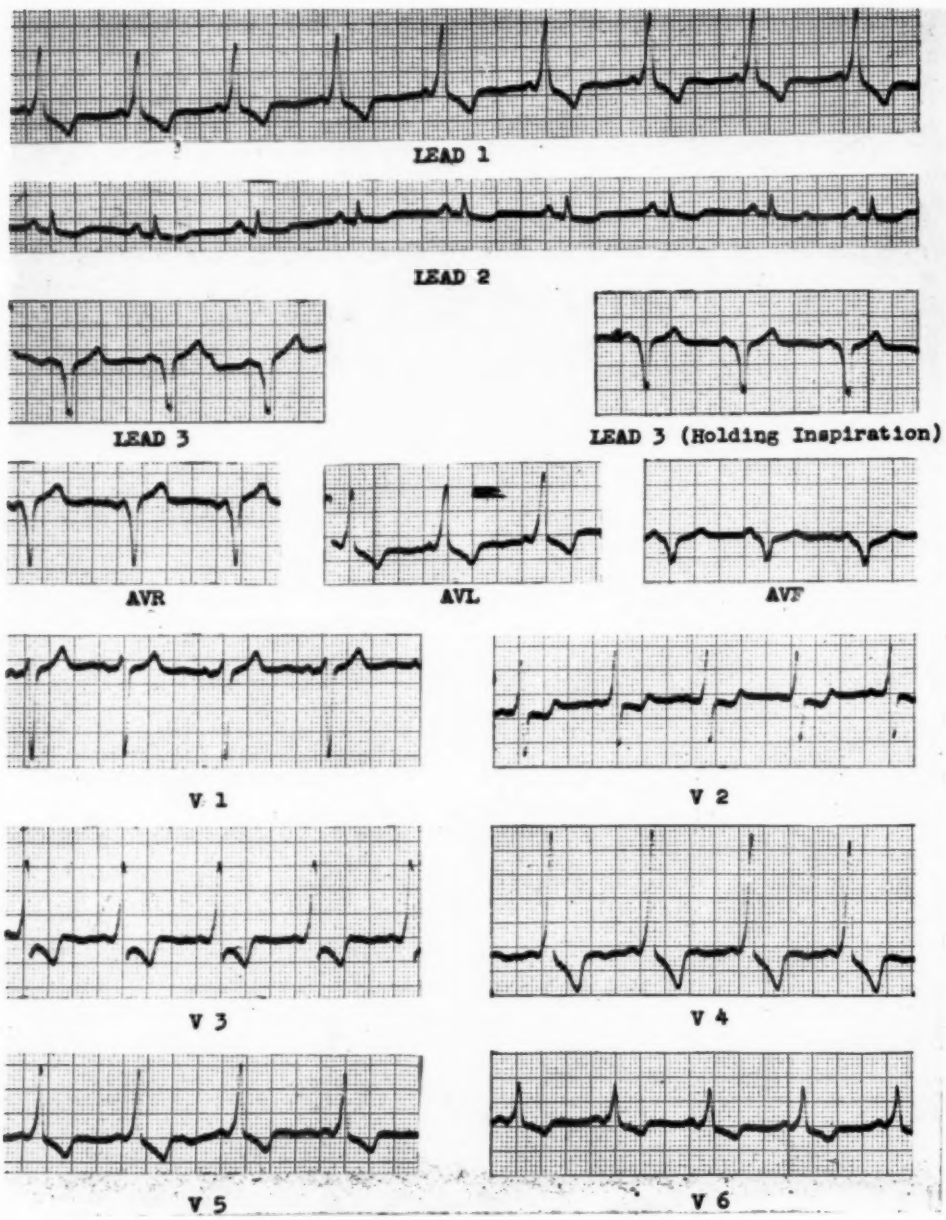

Fig. 3.—Electrocardiogram of W. K. showing anomalous atrioventricular conduction.

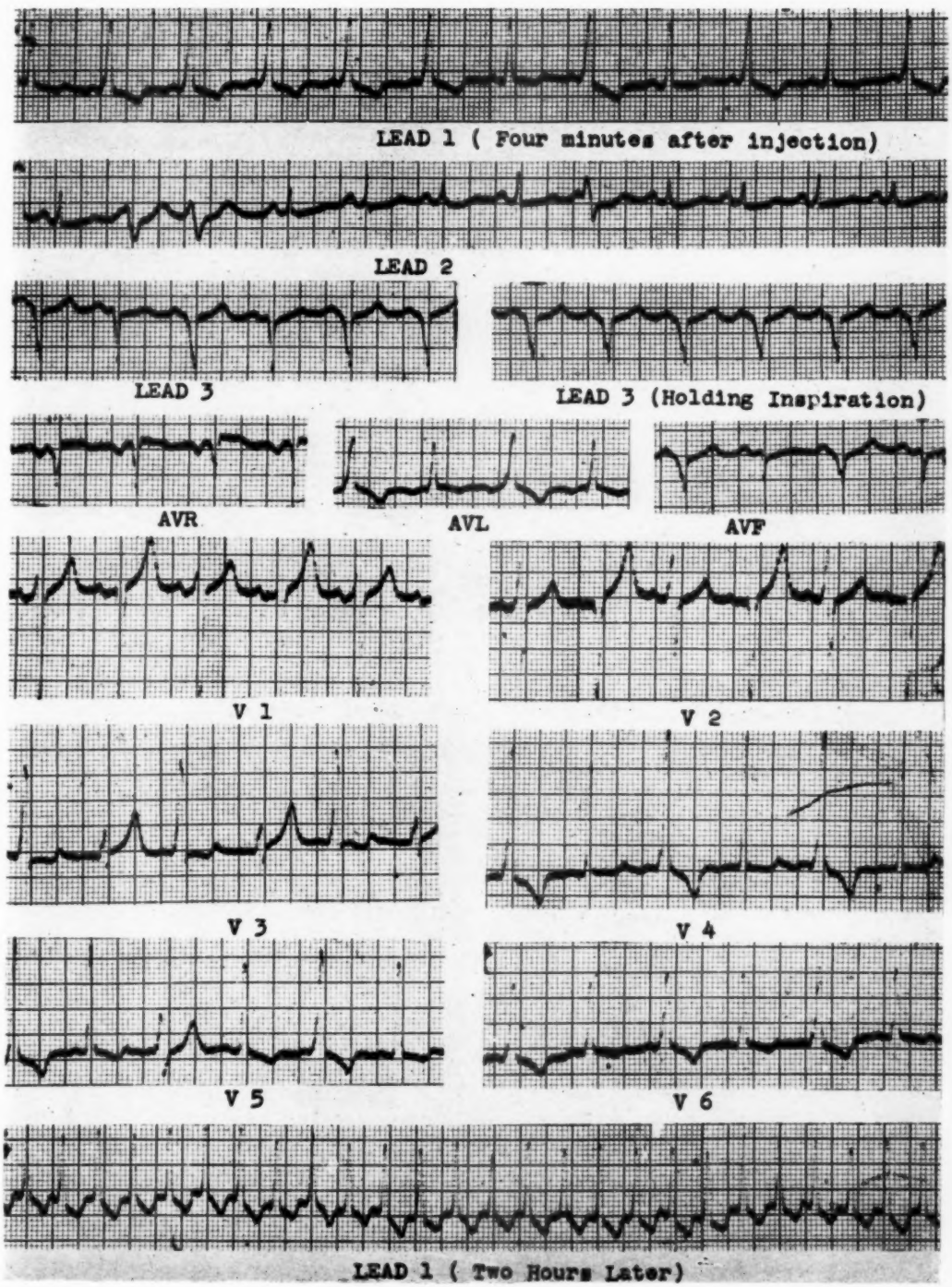

Fig. 4.—Electrocardiogram of W. K. following the intravenous injection of 1/50 gr. of atropine sulfate. Both anomalous and normal conduction are present, usually alternating in appearance. The latter have a lower voltage. The normal V_2 complexes have a QS appearance, whereas the anomalous complexes have an RS deflection. The normal complexes in V_4 have an upright T wave, and the anomalous complexes have a deeply inverted T wave. P-J is equal in both types of complex. Two hours later, the patient developed a supraventricular tachycardia which reverted to a normal rhythm following digitalization with Cedilanid.

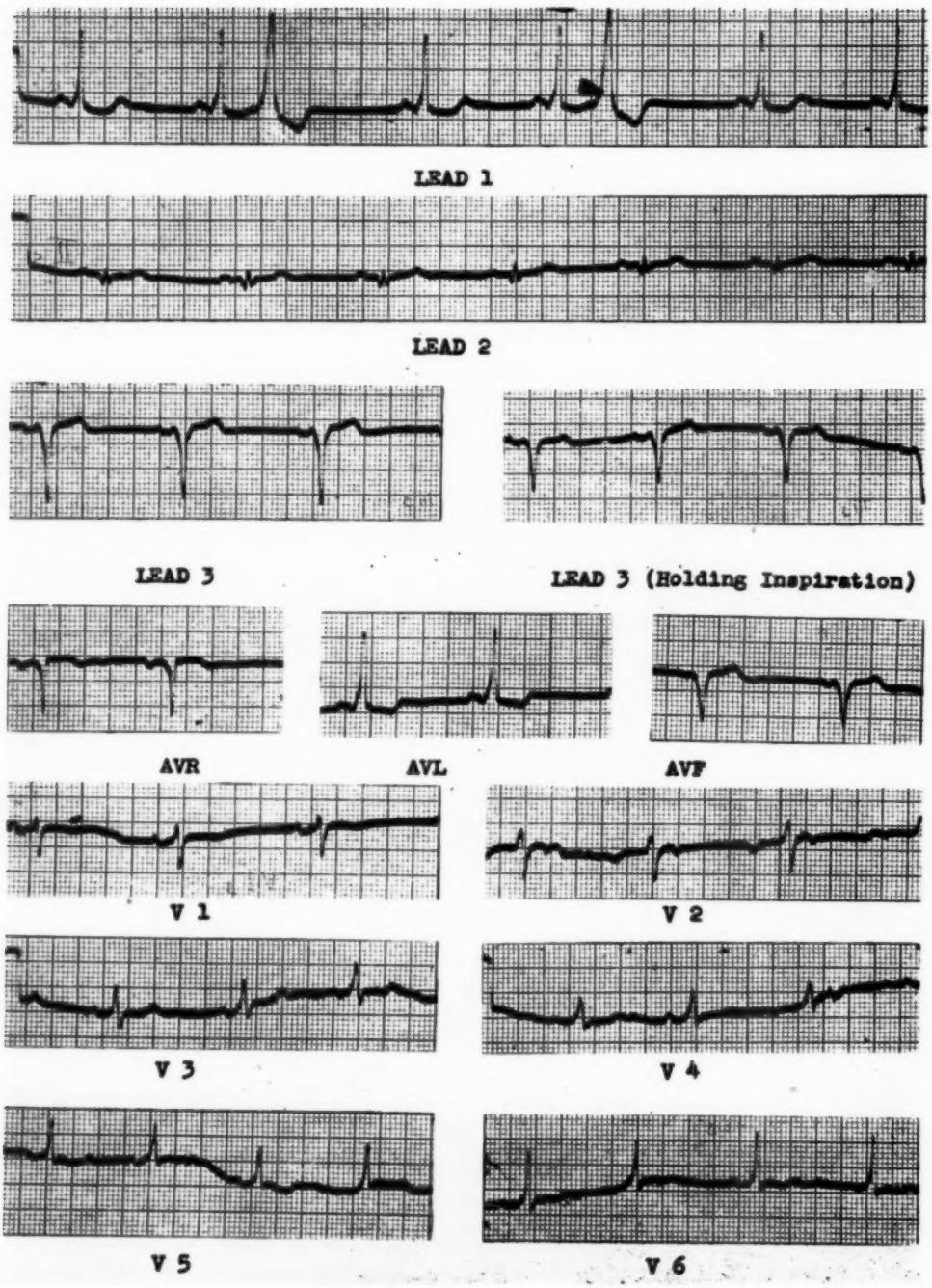

Fig. 5.—Electrocardiogram of F. G. showing anomalous atrioventricular conduction. The extrasystoles in Lead I are probably the result of retrograde conduction through the conduction bundle with re-entry into the right ventricle via the aberrant bundle.

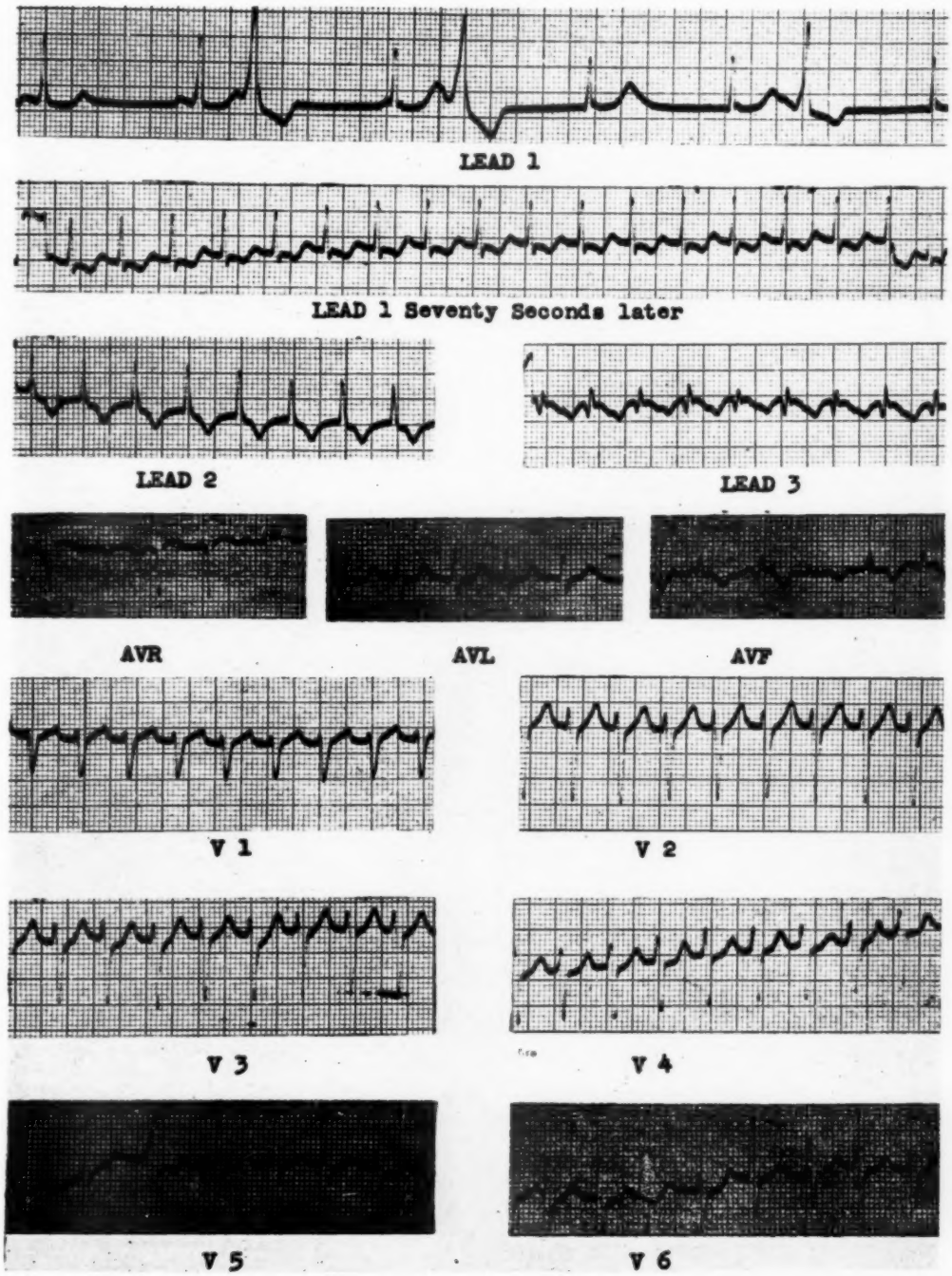

Fig. 6.—Electrocardiogram of F. G. following the intravenous injection of 1/75 gr. of atropine sulfate. A nodal rhythm gradually appears in Lead I with marked narrowing of the QRS complexes. The re-entry extrasystoles, however, are still present. Seventy seconds later, a supraventricular tachycardia appeared which subsided spontaneously.

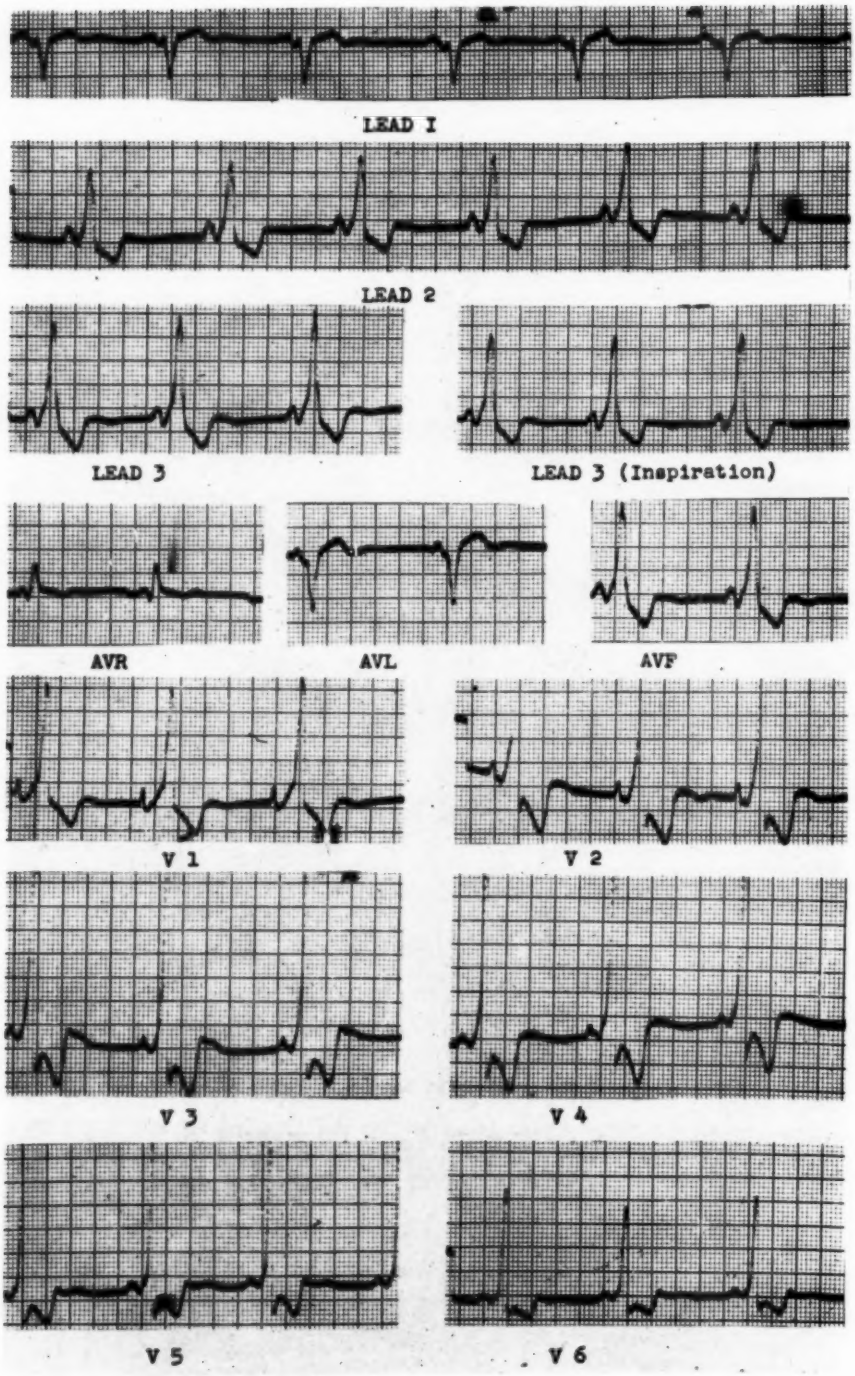

Fig. 7.—Electrocardiogram of H. V. showing anomalous atrioventricular conduction of unusual type due to the aberrant conducting tissue being on the left side, causing pre-excitation of the left ventricle. Electrocardiograms taken while a normal sinus mechanism was present showed both P-mitrale and P-pulmonale in addition to a right strain pattern.

QRS complex had a normal duration. This nodal rhythm persisted throughout Lead II. In Lead III a sinus mechanism was again established which persisted throughout the remainder of the tracing, although occasional complexes in the V leads resembled the fusion beats of anomalous conduction.

The nature of this syndrome was described to the patient who made a remarkable psychic recovery.

CASE 2.—W. K., a 48-year-old white man, had been admitted to the Los Angeles County Hospital on many occasions during the past ten years because of severe episodes of tachycardia usually accompanied by severe, crushing substernal pain. Electrocardiograms taken during these episodes showed both supraventricular and ventricular tachycardia which reverted to either a normal sinus mechanism or anomalous atrioventricular conduction.

Physical examination and fluoroscopy revealed only slight left ventricular hypertrophy and a soft mitral systolic murmur. There was no rheumatic history, and it was felt that the hypertrophy was secondary to the frequent episodes of tachycardia.

Fig. 8.—Electrocardiogram of H. V. Continuous record of Lead II taken 20 seconds after the intravenous injection of 1/50 gr. atropine sulfate. The QRS complexes are now 0.08 second in duration as the P waves slowly shift back and forth, at times resembling an upper and middle nodal rhythm and at other times a complete atrioventricular dissociation.

Electrocardiographic Studies.—Fig. 3 is a tracing showing anomalous atrioventricular conduction. Fig. 4 is a tracing taken after the intravenous administration of 1/50 gr. of atropine sulfate. Both anomalous and normal conduction were present, usually alternating in appearance. The latter had a lower voltage. The normal V_2 complexes had a QS appearance, whereas the anomalous complexes had an RS deflection. The normal complexes in V_4 had an upright T wave, and the anomalous complexes had a deeply inverted T wave. The P-J intervals in both types of complexes were equal. Approximately two hours after the administration of atropine sulfate, a supraventricular tachycardia appeared which responded to intravenous Cedilanid. This may have been due to the atropine sulfate.

CASE 3.—F. G., a 61-year-old white man, had been admitted to the Los Angeles County Hospital on several occasions because of paroxysmal tachycardia accompanied by dyspnea and

substernal pain. The tachycardia was of supraventricular origin. Physical examination and fluoroscopy revealed slight left ventricular hypertrophy with a soft apical systolic murmur. The episodes of tachycardia were the only explainable cause for the cardiac hypertrophy. The blood pressure was 140/90 mm. Hg.

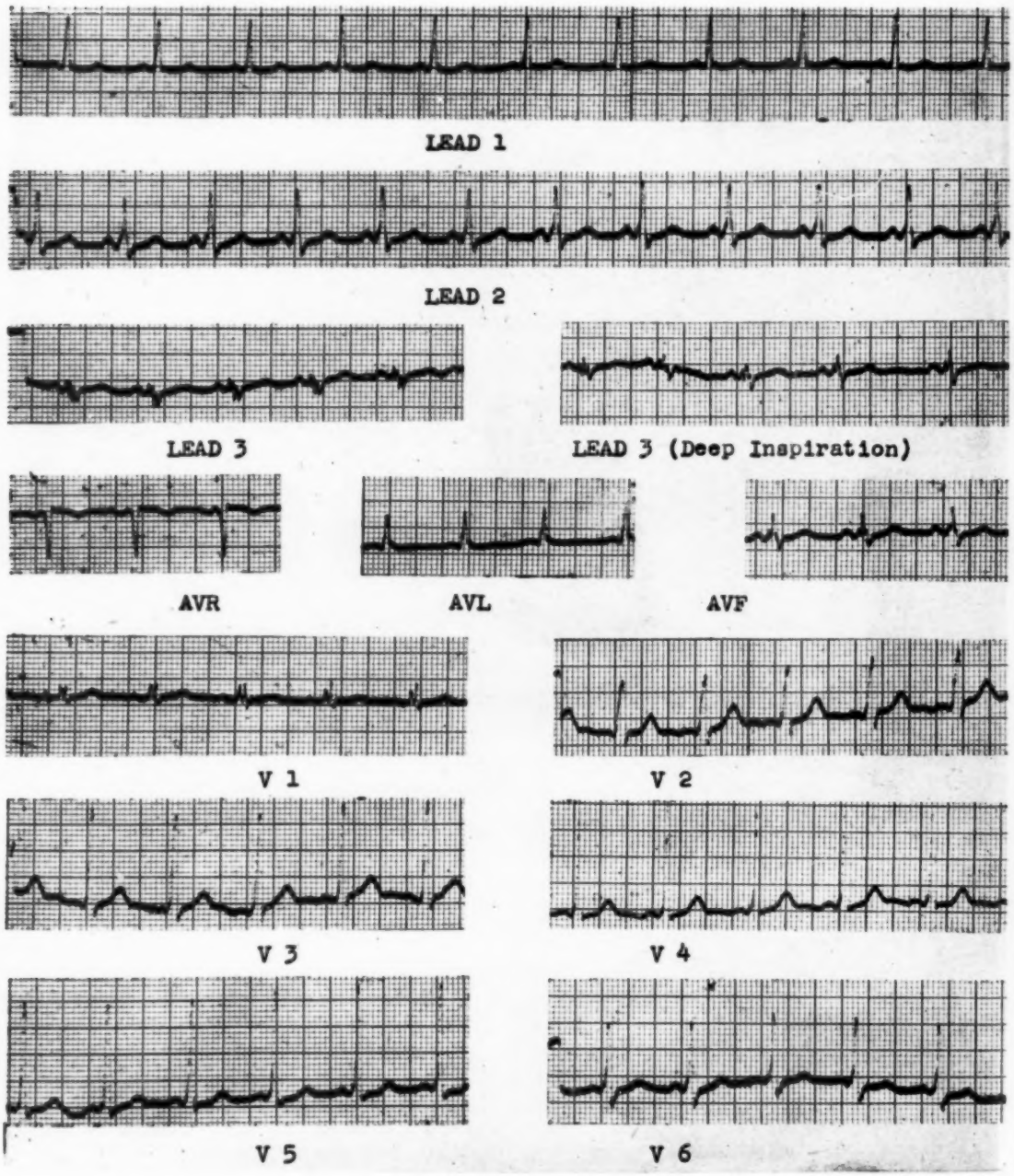

Fig. 9 —Electrocardiogram of J. D. showing anomalous atrioventricular conduction, which is best seen in Lead II where the P-R interval is 0.10 and the QRS complex measures 0.12 second.

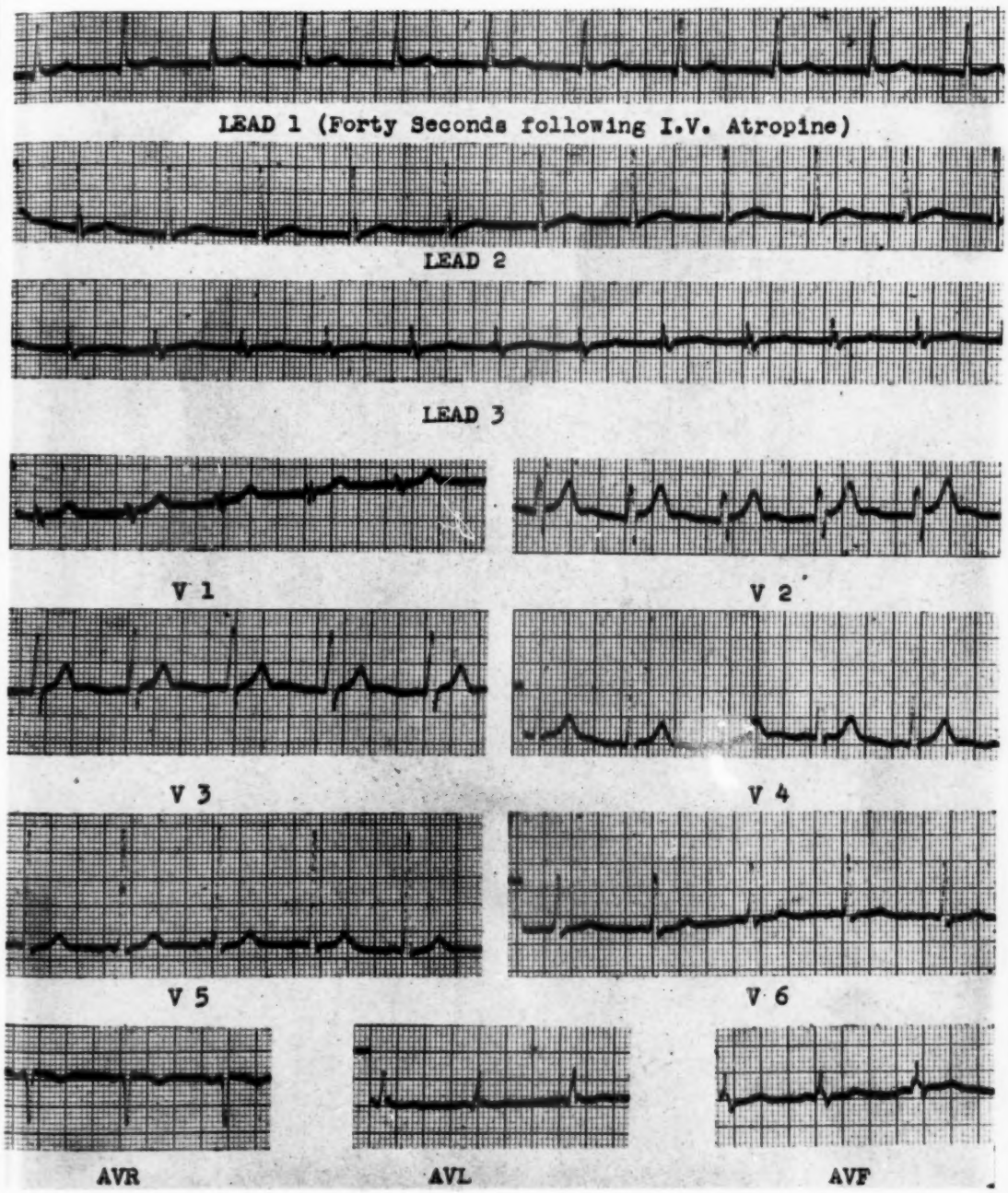

Fig. 10.—Electrocardiogram of J. D. following the intravenous injection of 1/75 gr. of atropine sulfate. A middle nodal rhythm is now present with a small Q_1, and the QRS complex measures only 0.08 second in duration.

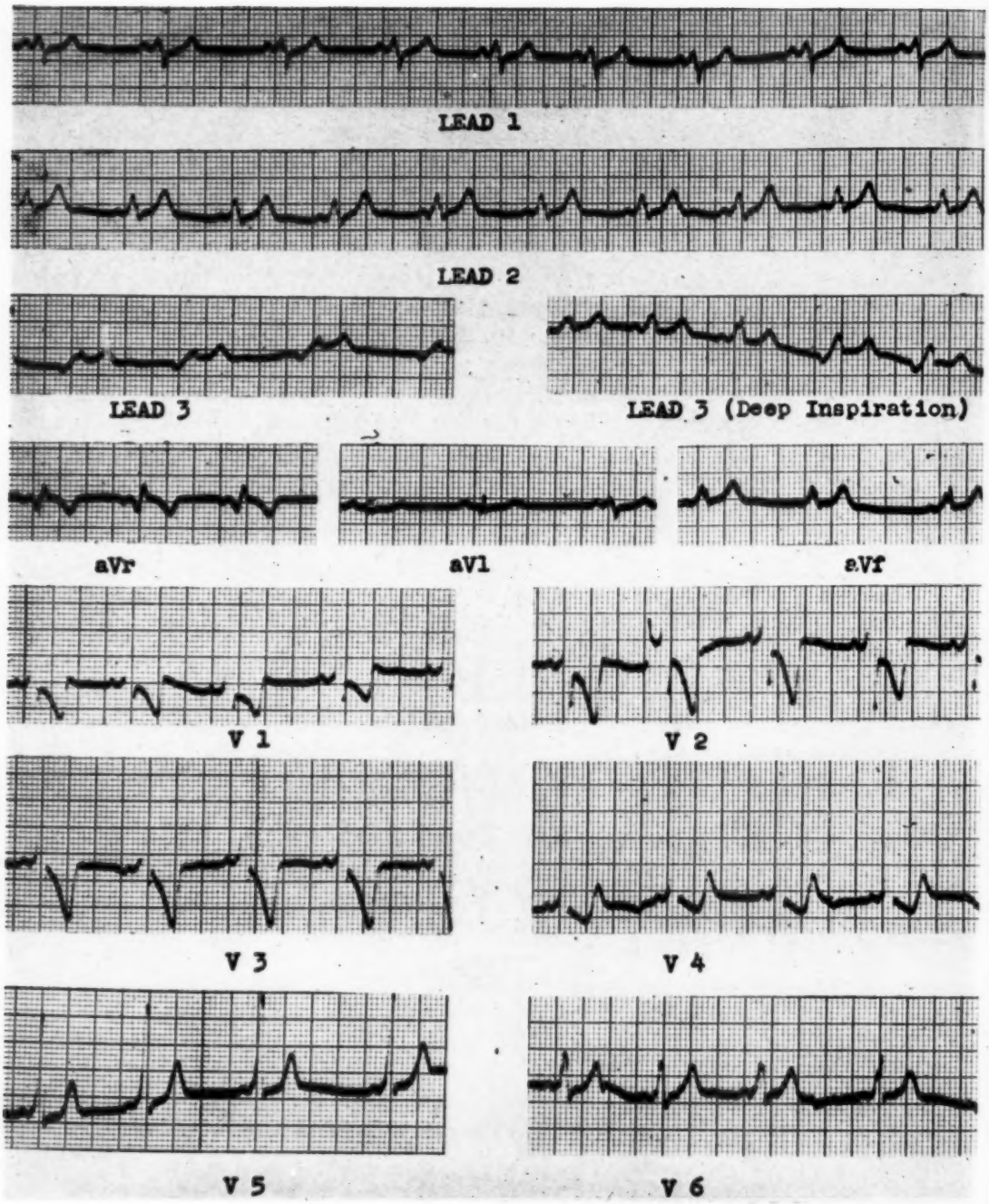

Fig. 11.—Electrocardiogram of J. F. showing anomalous atrioventricular conduction.

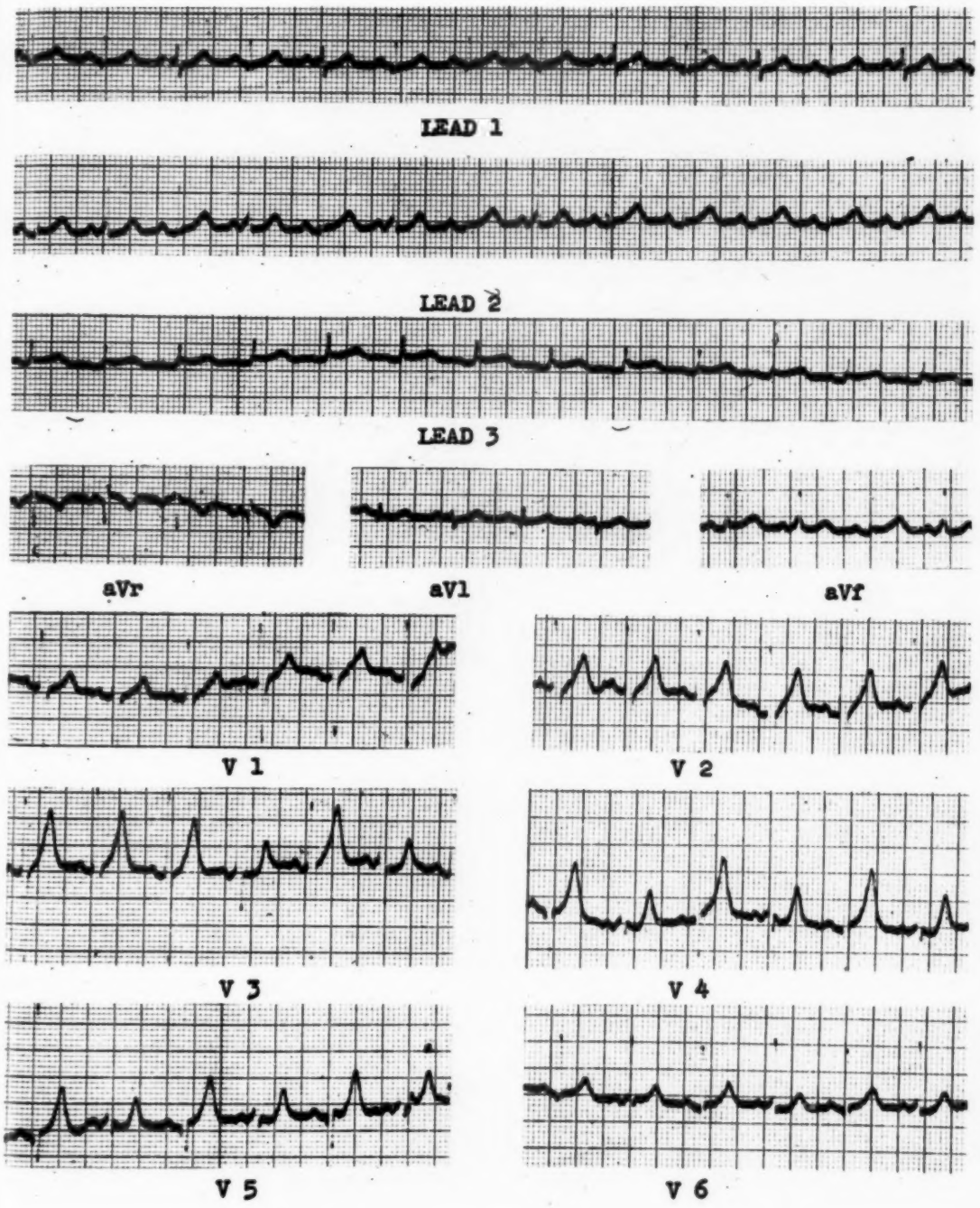

Fig. 12.—Electrocardiogram of J. F. following the intravenous injection of 1/75 gr. of atropine sulfate. In Leads I and II, both anomalous and normal conduction are present. In Lead III only normal complexes are seen. This is also true in V_1 and V_2. In V_3 two transitional complexes are present. This is also seen in V_4, V_5, and V_6.

Electrocardiographic Studies.—Fig. 5 is a tracing showing anomalous atrioventricular conduction. The extrasystoles present in Lead I were probably the result of retrograde conduction through the conduction bundle to the auricles with re-entry into the right ventricle through an aberrant bundle. Following the intravenous injection of 1/75 gr. of atropine sulfate, a nodal rhythm appeared with marked shortening of the QRS complex in Lead I (Fig. 6). The re-entry extrasystoles, however, were still present. Seventy seconds later, a supraventricular tachycardia appeared which persisted throughout all leads and subsided spontaneously shortly after. The QRS complexes seen in the tachycardia were of normal duration, and the axis had shifted to the right.

CASE 4.—H. V., a 31-year-old Mexican man, had been admitted to the Los Angeles County Hospital on numerous occasions because of attacks of paroxysmal tachycardia accompanied by substernal pain and hemoptysis. The patient had a history of rheumatic fever. Electrocardiographic tracings taken during his attacks showed supraventricular tachycardia, which either reverted to a normal sinus pattern or to anomalous atrioventricular conduction.

Physical examination revealed the patient to have a mitral stenosis and regurgitation, aortic stenosis and regurgitation, and an auricular septal defect. This was substantiated by fluoroscopy. The blood pressure was 100/40 mm. Hg. An electrocardiogram taken while a normal sinus mechanism was present showed both P-mitrale and P-pulmonale with right heart strain.

Electrocardiographic Studies.—Fig. 7 shows anomalous atrioventricular conduction of unusual type in that the aberrant bundle was on the left side of the heart, causing pre-excitation of the left ventricle. Fig. 8 was taken immediately following the intravenous injection of 1/50 gr. of atropine sulfate. The QRS complexes were now 0.08 second in duration as the P waves slowly shifted back and forth, at times resembling an upper and middle nodal rhythm and at other times a complete atrioventricular dissociation.

The patient was discharged to be followed in the cardiac clinic with a diagnosis of rheumatic and congenital heart disease, Lutembacher's syndrome.

CASE 5.—J. D., a 41-year-old white man, following routine electrocardiographic studies was told that he had either coronary artery disease or an unusual type of bundle branch block. This diagnosis was later changed to anomalous atrioventricular conduction. Physical examination and fluoroscopy were negative.

Electrocardiographic Studies.—Fig. 9 shows anomalous atrioventricular conduction which is best seen in Lead II where the P-R interval was 0.10 second, and the QRS complex measured 0.12 second. Fig. 10 was taken immediately following the intravenous injection of 1/75 gr. of atropine sulfate. A middle nodal rhythm was present, and the QRS complex now had a duration of 0.08 second. The aberrant conduction pattern closely resembled the normally conducted complexes.

CASE 6.—J. F., a 10-year-old white boy, had been admitted on numerous occasions to the Children's Hospital of Los Angeles because of attacks of paroxysmal tachycardia accompanied by substernal pain, nausea, and vomiting. Electrocardiographic tracings taken during such episodes revealed supraventricular tachycardia.

Physical examination was negative except for a venous hum, heard in the left infraclavicular area, that disappeared with left jugular vein pressure and a functional apical systolic murmur.

Electrocardiographic Studies.—Anomalous atrioventricular conduction was present in Fig. 11. Fig. 12 is an electrocardiographic tracing following the intravenous injection of 1/75 gr. of atropine sulfate. In Leads I and II, both anomalous and normal conduction were present. In Lead III only normal sinus complexes were seen. A deep S wave was present in the abnormal complexes in Lead I. Marked differences were also present in the chest leads. P-J was equal in both anomalous and normal conduction.

DISCUSSION

Katz and Kaplan[8] have emphasized that a short P-R interval with a prolonged QRS complex can exist in the presence of nodal rhythm with intraventricular block. Thus a diagnosis of anomalous atrioventricular conduction cannot be made unless the electrocardiographic pattern can be converted to a normal one. In the experience of the authors, this is most easily done by the use of large doses of intravenous atropine sulfate.

Atropine can have five effects on anomalous atrioventricular conduction: (1) it can have no effect;[1,7,13,14,18] (2) it can revert anomalous conduction to a normal sinus conduction mechanism;[7,11,12,15,20,22] (3) it can establish a pattern in which the QRS complex is shortened, but the P-R interval remains unchanged (nodal rhythm?);[1,6,9,14] (4) it can establish a nodal rhythm with shortening of the QRS complex duration;[3,5,7] and (5) it can cause complete atrioventricular dissociation.[3]

In some cases atropine sulfate appears to act upon the left vagus nerve, partially relieving the atrioventricular node of vagal influence, while the sinus node remains under vagal control. Thus the atrioventricular node becomes dominant, resulting in a nodal rhythm. This lowers the origin of the cardiac impulse below the level of the aberrant conduction, resulting in a normally conducted ventricular complex. Atropine succeeded in producing a QRS complex of normal duration in each case in this series. The probable reason that some investigators failed to achieve such an effect is the fact that they failed to administer the drug intravenously and in large enough doses. Following the administration of atropine sulfate intravenously, Cases 2 and 6 reverted to a normal conduction pattern, and Cases 3 and 5 established a nodal rhythm in which the QRS became normal in duration. Case 1 developed a normal sinus mechanism, then a nodal rhythm with a normal QRS complex, which in turn reverted to a normal sinus mechanism. Both nodal rhythm and complete atrioventricular dissociation with marked narrowing of the QRS complexes occurred in Case 4. Thus anomalous atrioventricular conduction was proved in the six cases presented in this series.

Cases 2 and 3 developed supraventricular tachycardia following the use of atropine intravenously, but this complication was easily controlled. Then, too, the question arises as to whether this tachycardia would have occurred without the use of atropine. Case 2 had intravenous injections of atropine sulfate on two later occasions with no reappearance of the tachycardia. Fox, Travell, and Molofsky also report tachycardia following the diagnostic use of atropine.[6] The authors do not consider this complication serious enough to prohibit the use of atropine as a diagnostic aid in anomalous atrioventricular conduction.

Tamagna and associates[16] report that the diagnosis of acute myocardial infarction can be made by use of electrocardiographic tracings if the infarct is large and particularly if the right ventricle is prematurely activated. Small infarctions could not be diagnosed in the presence of anomalous atrioventricular conduction. These authors think that, when an infarction is suspected in the presence of anomalous atrioventricular conduction, an effort should be made to convert the conduction pattern to a normal one so that a definite diagnosis can be made. This is particularly true in that T waves are unstable[19] in anomalous conduction, and the complicating attacks of tachycardia can often be accompanied by substernal pain.[2,4,10,23] Only Case 5 of this series failed to have a history of tachycardia accompanied by substernal pain. Thus atropine sulfate may prove of value in ruling out myocardial infarction when a definite diagnosis is mandatory.

SUMMARY AND CONCLUSIONS

1. Six cases illustrating the physiological action of atropine sulfate on the cardiac mechanism in anomalous atrioventricular conduction have been presented.

2. Atropine sulfate, properly administered, is a definite diagnostic aid in the syndrome of anomalous atrioventricular conduction.

REFERENCES

1. Barker, J. M.: Syndrome of Premature Ventricular Excitation in Which PR Interval Is Short and QRS Complex Is Prolonged, M. Ann. District of Columbia **15**:1-14, 1946.
2. Claggett, H., Jr.: Short P-R Interval With Prolonged QRS Complex: Allergic Manifestations and Unusual Electrocardiographic Abnormalities, Am. Heart J. **26**:55, 1943.
3. Duthie, R. J.: Wolff-Parkinson-White Syndrome: Mechanism, Brit. Heart J. **8**:96, 1946.
4. Eichert, H.: Wolff-Parkinson-White Syndrome Simulating Myocardial Infarction, Ann. Int. Med. **21**:907, 1944.
5. Fox, T. T.: The Production of Atrioventricular Rhythm in Man After the Administration of Atropine, Arch. Int. Med. **16**:989, 1915.
6. Fox, T. T., Travell, J., and Molofsky, L.: Action of Digitalis on Conduction in the Syndrome of Short P-R Interval and Prolonged QRS Complex, Arch. Int. Med. **71**:206, 1943.
7. Hunter, A., Papp, C., and Parkinson, J.: The Syndrome of Short P-R Interval, Apparent Bundle Branch Block, and Associated Paroxysmal Tachycardia, Brit. Heart J. **2**:107, 1940.
8. Katz, L. N., and Kaplan, L. G.: Unusual Forms of Rhythms Involving the A-V Node, Am. Heart J. **16**:694, 1938.
9. Klainer, M. J., and Joffe, H. H.: Short P-R Interval and Prolonged QRS Complex With Paroxysms of Ventricular Tachycardia, Ann. Int. Med. **24**:920, 1946.
10. Levine, S. A., and Beeson, P. B.: The Wolff-Parkinson-White Syndrome With Paroxysms of Ventricular Tachycardia, Am. Heart J. **22**:401, 1941.
11. Missal, M. E., Wood, D. J., and Leo, S. O.: Paroxysmal Ventricular Tachycardia Associated With Short P-R Intervals and Prolonged QRS Complexes, Ann. Int. Med. **24**:911, 1946.
12. Palatucci, O. A., and Knighton, J. E.: Short P-R Interval Associated With Prolongation of QRS Complexes: A Clinical Study Demonstrating Interesting Variations, Ann. Int. Med. **21**:58, 1944.
13. Roberts, G. H., and Abramson, D. I.: Ventricular Complexes of the Bundle Branch Type Associated With Short P-R Intervals, Ann. Int. Med. **9**:983, 1936.
14. Robinson, R. W., and Talmage, W. G.: Wolff-Parkinson-White Syndrome (Five Cases), Am. Heart J. **29**:569, 1945.
15. Stein, I.: Short P-R Interval and Prolonged QRS Complex, Ann. Int. Med. **24**:60, 1946.
16. Tamagna, I. G., Butterworth, J. S., and Poindexter, C. A.: Wolff-Parkinson-White Syndrome With Myocardial Infarction: An Experimental Study, Am. Heart J. **35**:948, 1948.
17. Tung, C. L.: Functional Bundle Branch Block, Am. Heart J. **11**:89, 1936.
18. Wedd, A. M.: Paroxysmal Tachycardia With Reference to Nomotropic Tachycardia and the Role of the Cardiac Intrinsic Nerves, Arch. Int. Med. **27**:571, 1921.
19. Wendkos, H. H., and Nadler, C.: Observations Concerning the Instability of the T Wave in the Wolff-Parkinson-White Syndrome, Proc. Am. Federation Clin. Research **3**:62, 1947.
20. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. **16**:1008, 1915.
21. Wilson, F. N.: The Production of Atrioventricular Rhythm in Man After the Administration of Atropine, Arch. Int. Med. **16**:989, 1915.
22. Wolff, L., Parkinson, J., and White, P. D.: Bundle Branch Block With Short P-R Interval in Young People Prone to Paroxysmal Tachycardia, Am. Heart J. **5**:685, 1930.
23. Wood, F. C., Wolferth, C. C., and Geckeler, G. D.: Histologic Demonstration of Accessory Muscular Connections Between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex, Am. Heart J. **25**:454, 1943.

THE ACTION OF ACETYL STROPHANTHIDIN IN RAPID CARDIAC ARRHYTHMIAS

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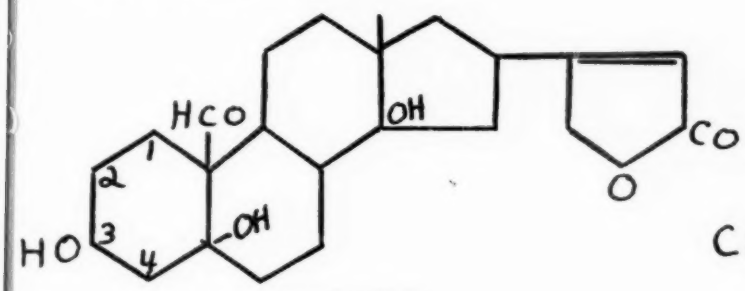
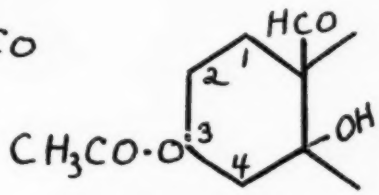
THE object of this study was to determine the effects of acetyl strophanthidin on rapid disorders of the heartbeat. This new substance acts with extraordinary speed, its influence often becoming manifest almost immediately after intravenous injection. The agent is not a glycoside, but rather a synthetic ester of the cardiac aglycone strophanthidin.

By taking advantage of the highly reactive properties of the secondary hydroxyl group at the carbon atom 3 position of aglycones, it has proved possible to prepare several synthetic esters and glycosides by interaction with various acids and glucose molecules.



Strophanthidin



Acetyl strophanthidin

Chen and Elderfield[1] have reported on several such derivatives of strophanthidin. The synthetic acetyl ester and three synthetic glycosides appear to be more potent than strophanthidin itself, and some of the synthetic glycosides are more potent than the related natural glycoside, cymarin. In similar fashion synthetic glycosides have been made from the aglycones digitoxigenin, digoxigenin, and periplogenin, and these derivatives appear to be more active than digitoxin, digoxin, and periplocymarin, respectively.[2]

Of the synthetic esters of strophanthidin which have been studied, the acetyl homolog was the most promising.[3] It is too poorly absorbed for peroral use and must be given intravenously. It has a cat unit value of about 0.2 mg. per kilogram.[4] Gold and his collaborators[5] compared this ester with ouabain in seven

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cases of auricular fibrillation. In general, they found that it acted similarly to ouabain, but excelled it in speed of action and wore off much sooner.

The present report concerns certain effects of this new drug as shown in 154 trials on 125 patients. The group comprised the following types of heart disease: hypertensive, arteriosclerotic, 79; rheumatic, 22; unknown, probably arteriosclerotic, 2; congenital (interatrial defect), 1; thyrotoxic, 1; cor pulmonale, 2; and no demonstrable heart disease, 18.

The rhythmic mechanisms at the time acetyl strophanthidin was given were as follows: regular sinus rhythm, 26; sinus tachycardia, 11; supraventricular tachycardia, 12; His bundle tachycardia, 1; auricular flutter, 11; and auricular fibrillation, 74. Signs of congestive failure, chiefly of mild to moderate severity, were present in ninety-four patients.

METHOD

The resting ventricular rate was determined by control electrocardiograms of at least 30 seconds length, as well as by counting the apex beat or the galvanometer deflections for 2 minutes prior to injection of acetyl strophanthidin. Subsequent observations included similar records every minute or two for the first quarter-hour and subsequently at longer intervals, according to the character of response.

The drug was available in 2 c.c. ampules containing 3 cat units (approximately 0.6 mg.). The doses used were usually 1.2 mg. for patients not under the influence of digitalis and smaller amounts (0.2 to 0.6 mg.) for those known or suspected to be under current digitalis therapy. In several instances of auricular flutter (Cases 103, 112, 113, and 117) and fibrillation (Cases 25, 60, and 111) fractional doses were given at intervals of 10 to 40 minutes in order to avoid or minimize intoxication.

In twenty-five trials the drug was given in 10 c.c. of physiological saline; in all the others, it was used undiluted. Administration was intravenous and given over a period of 1 to 2 minutes.

The onset of action was arbitrarily chosen as the point at which a 20 per cent decline in ventricular rate occurred in order to avoid the inclusion of equivocal data.

RESULTS

Regular Sinus Rhythm.—Effective slowing occurred in seven patients, an increase in rate in six patients, and no significant change in rate in the remaining thirteen. There was no apparent correlation between congestive failure and change in rate. In two patients slowing was due to abolition of ventricular premature systoles present at the time of injection. These premature beats returned after an hour. Sinus arrhythmia, when present, was usually intensified.

Sinus Tachycardia.—The only clear-cut effect in the group of eleven cases was in a patient with paroxysmal sinus tachycardia (Case 41, Table III). The effect was distinctly toxic, consisting of incomplete atrioventricular block with dropped beats, and in a later trial consisting of 2:1 block and also a transient period of complete dissociation with idioventricular rhythm.

Supraventricular Tachycardia.—Of the twelve patients eleven reverted to sinus rhythm which was maintained for at least a week. Of these, seven reverted in one to 3 minutes, one in 4 minutes, one in 8 minutes, one in 20 minutes, and one in 50 minutes. The refractory case was one of auricular tachycardia with high-grade atrioventricular block. All twelve patients in this group had organic heart disease.

His Bundle Tachycardia.—In one patient no change occurred after 1.2 mg. of acetyl strophanthidin.

Auricular Flutter.—All eleven patients showed distinct responses of the ventricular rate as detailed in Table I. In several instances the arrhythmia had appeared in patients who were receiving maintenance doses of oral digitalis preparations. In these (Cases 103, 112, 113, and 117) acetyl strophanthidin was given in doses of 0.2 to 0.4 mg. at intervals of 10 to 20 minutes.

TABLE I. THE EFFECT OF ACETYL STROPHANTHIDIN ON THE VENTRICULAR RATE IN AURICULAR FLUTTER

CASE	DOSE (MG.)	CONTROL RATE		INITIAL EFFECT		PEAK EFFECT	
		AURICULAR	VENTRICULAR	TIME (MINUTES)	VENTRICULAR RATE	TIME (MINUTES)	VENTRICULAR RATE
1 (2/26/49)	1.2	214	90	3	68	7	52
1 (12/ 8/49)	1.2	230	110	5	80	10	60
14	0.3	273	136	40	115	45	105
16	1.0	316	158	10	108	50	100
27	1.2	230	230	2	115	50	100
74 (11/27/49)	1.2	332	166	4	135	15	120
74 (12/ 4/49)	1.5	332	166	2	130	10	85
74 (12/11/49)	1.8	332	166	2	130	10	84
103	1.2	320	160	20	120*		
108 (3/27/50)	1.2	300	150	3	75	45	75
108 (4/26/50)	1.5	250	96	2	76	6	64
112	1.0	316	158	21	92	60	88
113	1.2	300	150	13	108	15	105
116 (5/ 4/50)	1.0	214	214	2	107	2	107
116 (5/ 5/50)	0.6	214	122	8	96	37	96
117	0.8	316	158	16	100	30	79

*Sinus tachycardia. See text and Figs. 1 and 2.

In only one instance was the flutter mechanism itself affected (Case 103). Twenty minutes after the third dose of 0.4 mg., sinus tachycardia appeared. Then ensued a period of rhythmic instability, including sinus rhythm, auricular premature systoles, auricular flutter, and auricular fibrillation. Standard and esophageal electrocardiograms are shown in Figs. 1 and 2. At the end of 2 hours 1.5 mg. digoxin was given orally, and the next day normal rhythm with occasional auricular extrasystoles was established.

Auricular Fibrillation.—Of the whole group of seventy-four cases, nineteen were definitely paroxysmal in nature. All nineteen paroxysms occurred in patients known to have had normal rhythm up to the onset of fibrillation. They were associated with a variety of disorders, including heart disease, neoplastic

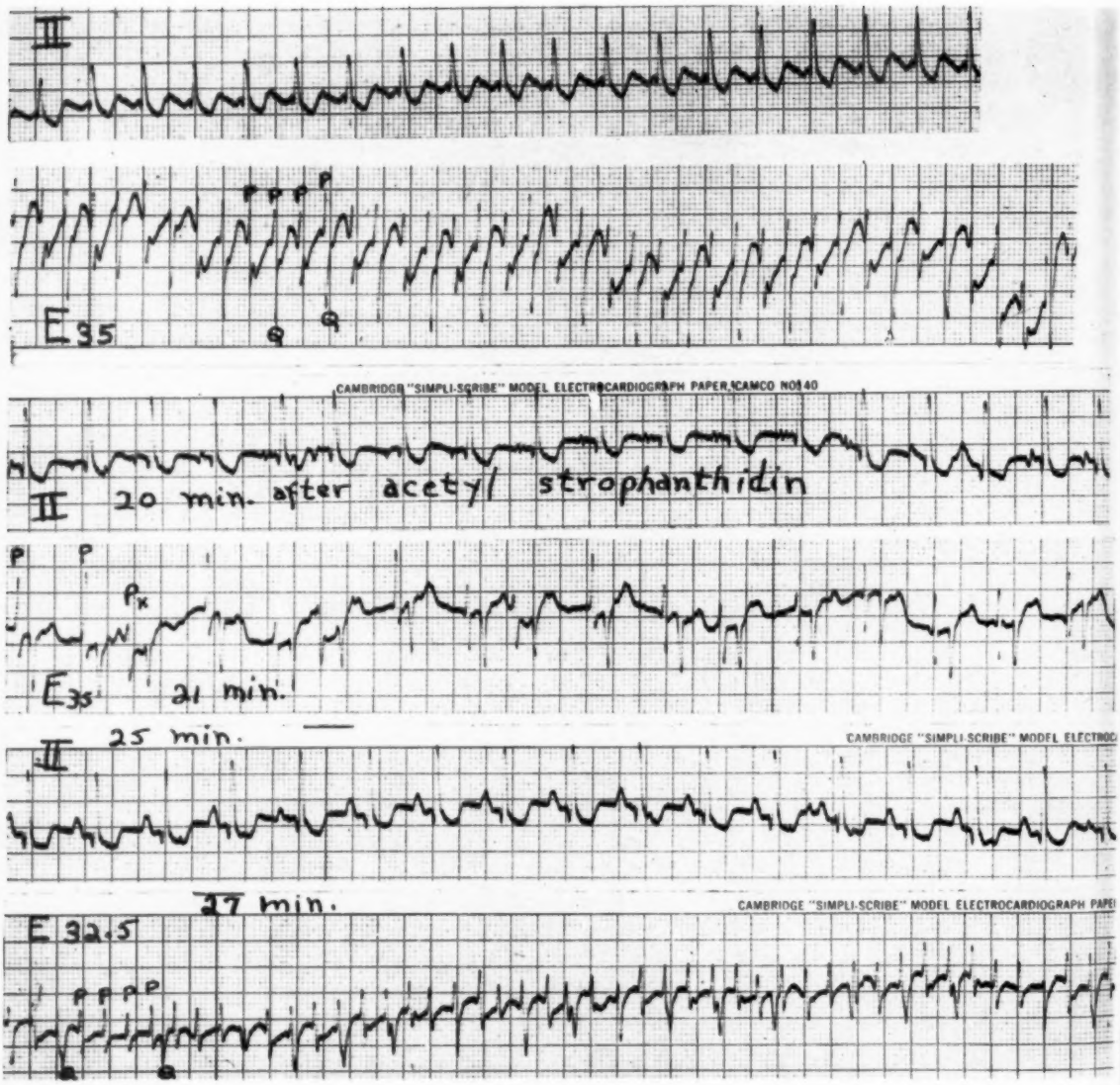

Fig. 1 (Case 103).—Response of a case of 2:1 auricular flutter to acetyl strophanthidin. The letter *E* designates an esophageal lead, the subscript denoting the distance in centimeters from the anterior nares. Note the presence of auricular ectopic beats (P_x) after sinus activity appears in the 21 minute record and the reappearance of flutter in 27 minutes.

disease, severe trauma, acute thromboembolic episodes, severe infections, and postoperative conditions. In seventeen of the patients acetyl strophanthidin had no effect at all. In one patient it slowed the ventricular rate from 160 to 120 in 15 minutes and to 100 in 30 minutes. In 6 hours normal rhythm appeared. In a second patient, a paroxysm of auricular fibrillation occurred during cardiac catheterization, while the catheter tip was in the pulmonary artery. The catheter was withdrawn, and acetyl strophanthidin was given in doses of 0.6

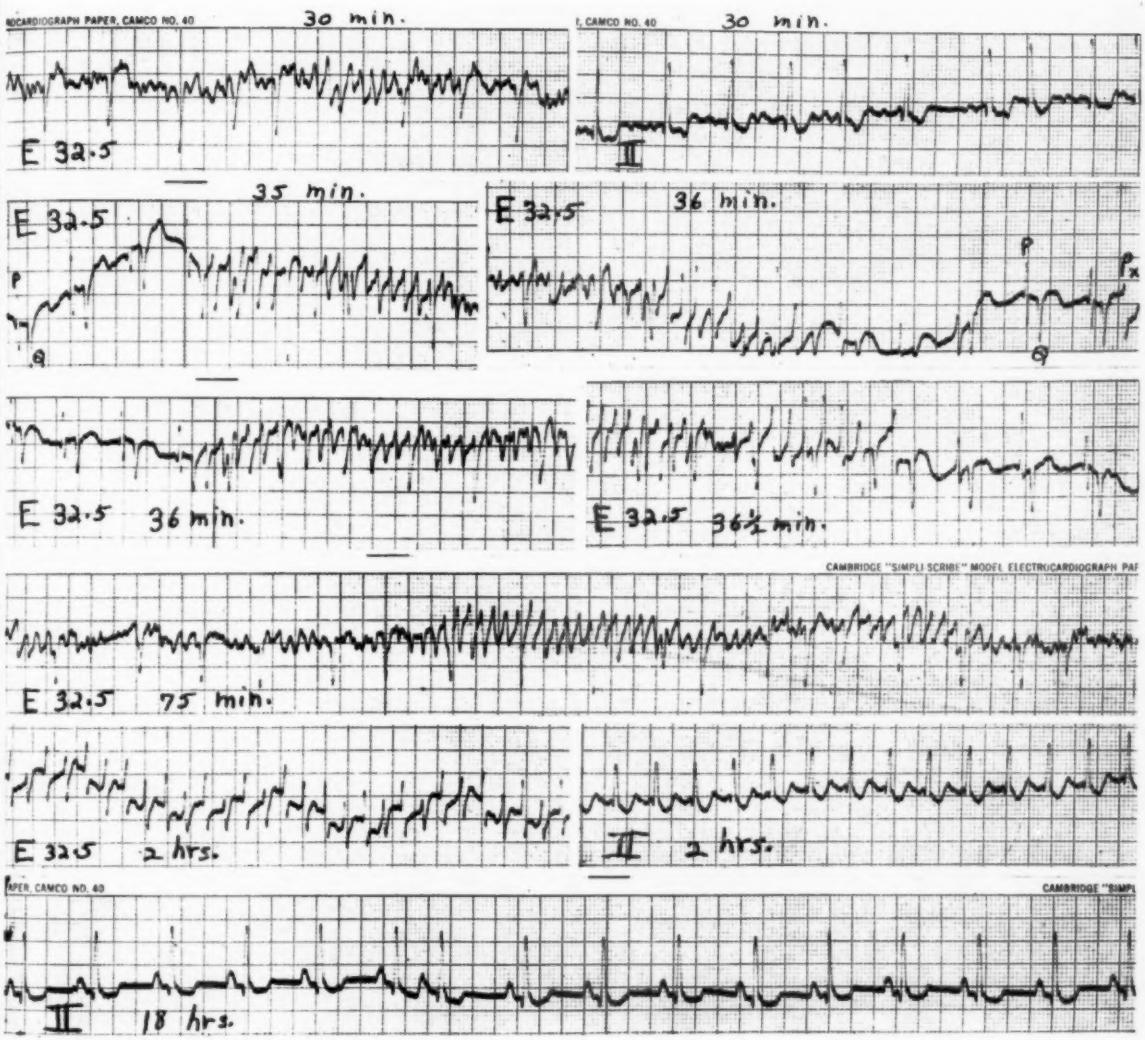

Fig. 2 (Case 103).—Two onsets and offsets of auricular fibrillation between 35 and 36½ minutes after acetyl strophanthidin. There was a return to flutter in 2 hours, and reversion to normal rhythm in 18 hours (16 hours after 1.5 mg. digoxin had been given).

mg. every 10 minutes. Thirteen minutes after the third dose, the ventricular rate fell from 180 to 70. It varied from 70 to 110 for the next 15 minutes, during which time the auricular deflections often resembled flutter. Oral digoxin, 1.5 mg., was then given, and within a few hours normal rhythm supervened.

Of the fifty-five patients with chronic fibrillation, nine failed to respond adequately. Six of the nine reacted with definite slowing, but of no more than 10 to 15 per cent, though they subsequently came under good control with oral digitalis preparations.

The remaining forty-six patients with chronic auricular fibrillation all responded sharply. The results are detailed in Table II.

TABLE II. THE EFFECT OF ACETYL STROPHANTHIDIN ON THE VENTRICULAR RATE IN CHRONIC AURICULAR FIBRILLATION

CASE	DOSE (MG.)	CONTROL RATE	INITIAL EFFECT		PEAK EFFECT		LATER EFFECT	
			TIME (MINUTES)	RATE	TIME (MINUTES)	RATE	TIME (MINUTES)	RATE
5	0.6	140	2	110	10	80	55	90
7	1.2	132	4	102	15	85	60	92
9	1.2	180	2	148	15	100	30	130
11	1.2	130	1	106	15	62	30	70
12	0.6	110	2	85	25	55	60	80
21	1.2	150	2	120	7	90	120	90
22	1.2	106	2	80	8	70	75	80
26	1.2	147	4	120	16	56	72	80
28	1.2	144	2	114	30	100	120	126
29	0.6	147	3	121	8	105	120	118
31	0.6	158	3	124	10	80	18 hr.	144
32	0.6	156	6	108	10	72	20	84
34	0.6	183	1	137	5	108	90	116
35	1.2	160	2	130	6	100	60	120
40	0.6	160	2	130	8	110	40	160
42	0.6	190	1	150	5	90	12 hr.	180
47	1.2	190	5	150	7	130	40	140
48 (9/27/49)	0.6	195	7	150	20	120	60	150
48 (10/24/49)	1.2	200	3	160	8	120	40	140
48 (1/ 3/50)	0.6	110	5	70	4	70	20 hr.	84
52	0.6	120	2	108	17	102		
55	1.2	150	4	125	6	110	40	135
57	0.6	135	2	105	15	90	40	105
59	1.2	90	3	70	5	60	20	80
60	0.6	180	3	150	20	120	45	180
60*	0.6	180	3	150	30	130		
61	1.2	146	4	120	12	111	27	115
62	1.2	90	2	65	10	65	40	75
64	1.2	150	8	120	10	100	15	120
66 (11/ 5/49)	1.2	110	2	90	8	80	35	85
66 (11/10/49)	1.2	110	4	90	6	80	55	90
71	0.6	130	2	106	4	100	120	100
72	1.2	115	4	90	6	80	120	80
73	1.2	120	2	90	10	80	4 hr.	80
76	1.2	136	15	108	18	90	30	95
78	1.2	149	2	120	6	94	60	100
79	1.2	150	5	130	8	100	40	120
80	1.2	145	2	100	17	90	120	130
83	0.6	150	5	120	5	120	3 hr.	120
86	1.2	160	3	130	18	100	120	130
92	1.0	135	5	100	10	98	30	112
94 (2/ 9/50)	1.2	110	5	80	5	80	60	90
94 (4/ 4/50)	1.2	110	5	84	5	84	20	90
97	1.2	100	2	82	8	78	50	84
106	0.6	130	2	96	25	87	40	90
107	0.6	170	2	135	12	95	20	95
109	0.6	165	2	120	10	110	30	116
111	1.2	145	8	105	9	90	60	100
114	1.2	160	3	130	10	110	25	120
115 (4/ 8/50)	1.2	144	5	104	12	80	40	150
115 (4/19/50)	1.2	130	10	88	12	80	75	92
118	0.6	100	6	80	20	80	60	90

*Second dose given 45 minutes after first dose.

Effects on RS-T and T.—Very obvious changes did not occur often enough to warrant detailed analysis. The maximal changes appeared in association with intoxication (Cases 11, 32, 35, and 110 in Table III).

Toxic Effects.—Unequivocal evidence of toxicity occurred in thirty-three patients, in several of whom the manifestations were reproducible. The data are detailed in Table III, in which the patients are grouped according to their rhythms prior to administration of the drug. The most serious reactions were ventricular tachycardia (Cases 44, 53, and 60) and ventricular fibrillation. Fortunately, these were all transient, and no fatality attributable to the drug occurred in this series.

Accidental extravenous infiltration of some of the undiluted preparation occurred twice with but slight pain and no aftermath. Incidentally, in six instances ventricular premature systoles present at the time the drug was given were sharply reduced or abolished; in two other instances they were temporarily increased.

DISCUSSION

Method of Administration.—It is conceivable that the results of intravenous injection of a rapidly acting digitalis-like drug may depend in part upon the speed of injection. Most authorities recommend giving such substances very slowly on the grounds that the amount fixed by the heart is determined not only by the concentration in the blood, but also on the time during which the heart is exposed to the circulating drug.[6] Kisch[7] states that very slow injection of strophanthin may increase the effect, and he has accordingly given the drug in 500 c.c. of diluent over a period of 1 to 3 hours. In animals it is known that the lethal dose is smaller[8] and the toxic action more powerful,[9] the longer the injection lasts. Nevertheless, Östling[10] concluded from a study on twenty-three patients that the time factor has been exaggerated, and that there is no need to extend the time of injection beyond 1 minute to achieve full therapeutic effects. Indirect evidence favoring this view is found in the report of Bloomfield and associates.[11] They injected ouabain through intracardiac catheters over a period of 1 to 2 minutes and recorded blood pressure changes only 1 to 8 minutes later. The speed of response in the present study, in which less than 2 minutes were taken for administration, indicates that long injections are unnecessary so far as acetyl strophanthidin is concerned. Whether the high incidence of toxicity in the present series is attributable to the speed of injection is questionable, particularly in view of the prevailing beliefs mentioned above.

Acetyl strophanthidin in reduced doses was given to many patients who had been maintained on digitalis preparations up to the time of the trials. The efficacy of this procedure is apparent from the results obtained, and indeed this was anticipated on the basis of reported results with a cardiac glycoside.[12]

Speed of Action.—The short latent period is evident from inspection of the data in the tables. In the case of auricular flutter and chronic auricular fibrillation, ventricular slowing of 20 per cent or more occurred within 1 to 5 minutes, and peak effects within 16 minutes in four-fifths of the cases. It will be noted that the short latency is also reflected in the early onset of toxic manifestations; it was

TABLE III. TOXIC REACTIONS OF ACETYL STROPHANTHIDIN

CASE	RHYTHM	DOSE (MG.)	MANIFESTATION OF TOXICITY	ONSET (MINUTES)	DURATION (MINUTES)
36	R. S. R.	1.2	Frequent sinus arrests followed by interference dissociation with pseudoreciprocal rhythm	1½	30
37	R. S. R.	1.2	V.P.S. 25/100, frequency maintained	8	15
44	R. S. R.	1.2	Multifocal V.P.S. 38/57, progressing to runs of ventricular tachycardia up to 14 beats in length; vomiting	3	25
	R. S. R.	0.6	Next day, V.P.S. 8/100, gradually diminishing	4	11
45	R. S. R.	1.2	V.P.S. 6/49 to 9/51	2½	3
	R. S. R.	1.2	Next day, V.P.S. 24/78	4½	1
53	R. S. R.	1.2	V.P.S. 1/10, ventricular tachycardia, ventricular fibrillation, A-V dissociation	5	30
	R. S. R.	0.6	2 days later, frequent V.P.S. including some in salvos of 5	8	30
93	R. S. R.	1.2	Nausea, numbness of lips, V.P.S. 4/50	8	14
	R. S. R.	1.2	5 days later, same symptoms, V.P.S. 6/100	6	12
101	R. S. R.	1.2	P-R increase to 0.26 from 0.23; A.P.S. 1/20; later a salvo of six successive A.P.S.	6	24
	R. S. R.	1.2	2 days later, P-R 0.26 from 0.24; A.P.S. 1/20	8	6
110	R. S. R.	1.5	P-R 0.20 from 0.16; V.P.S. 4/100; ST depressed 2 mm. deeper than control; T negativity deepened 2.5 mm.	10	25
41	S. T.	1.2	Incomplete A-V block, dropped beats; aberrant ventricular complexes, not premature	3	42
	S. T.	1.2	2 days later, 2:1 A-V block; then transient idioventricular rhythm	3	37
4	S. V. T.	0.6	V.P.S. 50/100, gradually wearing off	7	43
58	A. T.	1.2	V.P.S. up to 16/100	2½	5
1	A. Fl.	1.2	V.P.S. up to 10/100	2½	27
74	A. Fl.	1.2	V.P.S. 4/100	5	10
	A. Fl.	1.2	8 days later, V.P.S. 16/100	3	20
113	A. Fl.	1.2	Vomiting	15	1
116	A. Fl.	0.6	V.P.S. 22/100 and vomiting	15	15
11	A. Fib.	1.2	V.P.S. 6/100 and sharp inversion of T wave	4	26
26	A. Fib.	1.2	V.P.S. 10/100, bifocal; vomiting	2	28
32	A. Fib.	0.6	Nausea; negativity of T increased 1 mm.	15	5
35	A. Fib.	1.2	Vomiting; ST depression 2 mm.	10	1
42	A. Fib.	0.6	V.P.S. 9/42	15	5
46	A. Fib.	1.2	V.P.S. 12/100	6	12
60	A. Fib.	1.2	Multifocal V.P.S. 16/100; then short runs of ventricular tachycardia	3½	17
64	A. Fib.	1.2	V.P.S. 8/100	12	6
76	A. Fib.	1.2	V.P.S. 50/100	18	7
79	A. Fib.	1.2	V.P.S. 6/100 and ectopic, nonpremature ventricular beats 6/100	4	12
80	A. Fib.	1.2	V.P.S. 8/100	5	10
94	A. Fib.	1.2	V.P.S. 8/86	3	40
97	A. Fib.	1.2	V.P.S. 18/107	2½	22
107	A. Fib.	0.6	V.P.S. 21/100	2	18
109	A. Fib.	0.6	V.P.S. 4/100	10	15
111	A. Fib.	1.2	V.P.S. 6/100	8	8
114	A. Fib.	1.0	V.P.S. 4/86	15	10
115	A. Fib.	1.2	V.P.S. 11/81; later, ventricular parasystole	10	18
	A. Fib.	1.0	11 days later, V.P.S. 16/100, followed by ventricular parasystole	12	15

R.S.R. = Regular sinus rhythm.
V.P.S. = Ventricular premature systoles expressed as a fraction, indicating the number of premature beats (numerator) among total beats counted (denominator).
A.P.S. = Auricular premature systoles.
S.T. = Sinus tachycardia.
S.V.T. = Supraventricular tachycardia.
A.T. = Auricular tachycardia.
A.Fl. = Auricular flutter.
A.Fib. = Auricular fibrillation.

5 minutes or less in over half the patients and not later than 18 minutes in any patient.

Duration of Effects.—The drug is undoubtedly dissipated very quickly. Gold and his collaborators[5] found most of the effects gone 4 hours after administration to seven patients. In the present study, less than half of the patients still had therapeutic levels of effects after 60 minutes (excluding the cases of supraventricular tachycardia). Only one patient had persistence of such effect for 3 hours. However, the data are insufficient to permit complete conclusions regarding the duration of action because of lack of uniformity in the follow-up observations.

Comparison With Other Rapidly Acting Preparations.—Ouabain is generally conceded to be the most rapidly acting of all the cardiac glycosides. Initial effects on the ventricular rate in auricular fibrillation are said to occur in 5 minutes,[13] or in 5 to 20 minutes.[14] However, it is not clear from these figures whether the decreases in rate might not have been minor, such as may occur spontaneously. For this reason, the criterion of a 20 per cent drop was arbitrarily selected in the present study as heralding the onset of action. More important are the peak effects, which are variously reported as occurring in 15 to 50 minutes,[14] 1 hour or more,[6] and 2 hours after ouabain.[15] A direct comparison of 1 mg. acetyl strophanthidin with 0.5 mg. ouabain (5 cat units of each) on seven patients showed that the new ester was definitely faster acting.[5] While the extent of effects was about the same, 70 per cent of the total effect developed by acetyl strophanthidin appeared in 5 minutes, as against 10 per cent for ouabain. Digoxin intravenously causes peak effects in 1 to 2 hours,[16] and lanatoside C is known to be quite similar in this regard.[17]

Sinus Mechanisms.—Acetyl strophanthidin action was not unlike digitalis action generally, so far as sinus rhythm and sinus tachycardia were concerned. That is, the effects were neither uniform nor striking, except when intoxication occurred.

Supraventricular Tachycardia.—The high incidence of successful termination of the ectopic rhythms, eleven out of twelve cases, was expected in the light of current experience with rapidly acting cardiac glycosides.[17-20] The speed with which reversion occurred was striking.

Of interest is the fact that in two of our patients the paroxysms appeared while the patients were on daily maintenance doses of digitalis preparations. In each instance the injection of 0.6 mg. of acetyl strophanthidin resulted in prompt restoration of normal rhythm. Subsequently, the maintenance doses of oral digitalis preparations for each patient were increased, and no further paroxysms occurred in the 4 and 5 month periods, respectively, which followed.

His Bundle Tachycardia.—Failure of our patient to revert to normal rhythm was not surprising, since digitalis cannot be expected to act in such fashion on infranodal arrhythmias.

Auricular Flutter.—In those instances where flutter appeared while the patients were receiving daily maintenance doses of digitalis preparations (Cases 103, 112, 113, and 117) and in two other instances where digitalis was started after flutter had appeared (Cases 14 and 116), the beneficial effect of acetyl

strophanthidin demonstrated the need for larger doses of digitalis. In every case the latter procedure was successful in maintaining the ventricular rate at proper therapeutic levels.

Case 103 is of special interest because the flutter mechanism was broken, though temporarily (Figs. 1 and 2). (The electrocardiographic features of this case have been described in detail in another communication[21] where it appears as Case 87.) It had been hoped that acetyl strophanthidin would be more successful in converting auricular flutter to fibrillation or normal rhythm. Such conversions have been reported after single doses of lanatoside C.[17,22]

Auricular Fibrillation.—The failure of the new drug in most of the cases of paroxysmal fibrillation was not unexpected, for it is common experience that this type of fibrillation is not ordinarily responsive to digitalis preparations. The case which occurred during cardiac catheterization was of interest, since this arrhythmia is rarely encountered during the procedure. In a recent series of fifty cases studied by continuous electrocardiographic recording during cardiac catheterization, practically all other arrhythmias were seen except auricular fibrillation,[23] although in an earlier series it occurred in two out of forty-two cases.[24]

The results in the responsive patients were similar in kind to those after any digitalis preparation, but they were much faster in appearance and in dissipation. It is noteworthy that no case of chronic fibrillation was converted. Yet such conversions have been reported following intravenous administration of cardiac glycosides.[17,18]

Toxicity.—The outstanding effect of this new agent, besides its unusually short latency and rapid dissipation, is its toxic action. Evidence of acute intoxication occurred in one out of every four subjects. Ominous toxic rhythms—ventricular tachycardia and ventricular fibrillation—occurred in three patients, not one of whom had received any digitalis preparation for at least 4 weeks prior to receiving acetyl strophanthidin. The case of ventricular fibrillation will be reported in detail in a separate communication.

One patient (Case 93) had numbness of the lips as a toxic symptom on two occasions. Similar symptoms have been recently reported as lesser known manifestations of digitalis toxicity.[25]

It is believed that the incidence of toxicity has been higher with acetyl strophanthidin than with other intravenous digitalis preparations in general use. Therefore, the new agent should be confined to further experimental use and not introduced into clinical practice at this time.

SUMMARY AND CONCLUSIONS

1. Acetyl strophanthidin, a synthetic ester of the cardiac aglycone strophanthidin, was given to 125 patients in 154 trials.
2. Its effects appeared with unusual speed, generally in 1 to 5 minutes.
3. The peak of action occurred mostly within 16 minutes.
4. The effects wore off within an hour or two.
5. Supraventricular tachycardias (eleven out of twelve cases) were very rapidly restored to normal rhythm.

6. One case of auricular flutter out of eleven was converted, but the effect was temporary.

7. Acute intoxication occurred in one out of every four patients, in some instances with ominous toxic rhythms.

8. It is therefore concluded that this agent may have value in investigative work, but that its toxicity precludes its application to clinical practice.

REFERENCES

1. Chen, K. K., and Elderfield, R. C.: Synthetic Derivatives of Strophanthidin, J. Pharmacol. & Exper. Therap. **76**:81, 1942.
2. Chen, K. K., Elderfield, R. C., Uhle, F. C., and Fried, J.: Synthetic Glycosides of Digitoxigenin, Digoxigenin, and Periplogenin, J. Pharmacol. & Exper. Therap. **77**:401, 1943.
3. Gold, H., Otto, H. L., Modell, W., and Halpern, S. L.: Behavior of Synthetic Esters of Strophanthidin, the Acetate, Propionate, Butyrate, and Benzoate, in Man, J. Pharmacol. & Exper. Therap. **86**:301, 1946.
4. Steldt, F. A., Anderson, R. C., Maze, N., and Chen, K. K.: Action of Strophanthidin-3-propionate, -butyrate, and benzoate, Proc. Soc. Exper. Biol. & Med. **53**:198, 1943.
5. Gold, H., Modell, W., Kwit, N. T., Shane, S. J., Dayrit, C., Kramer, M. C., Zahn, W., and Otto, H. L.: Comparison of Ouabain With Strophanthidin-3-Acetate by Intravenous Injection in Man, J. Pharmacol. & Exper. Therap. **94**:39, 1948.
6. Movitt, E. R.: Digitalis and Other Cardiotonic Drugs, New York, 1946, Oxford University Press.
7. Kisch, B.: Strophanthin, New York, 1944, Brooklyn Medical Press.
8. Maresh, G., and Farah, A.: Toxicity Ratios of Some Cardiac Glycosides as Influenced by the Experimental Time, Federation Proc. **5**:191, 1946.
9. Östling, G.: Determination of Cumulative Effect and Elimination of Cardiac Glycosides by Infusion Tests, Acta pharmacol. et toxicol. **3**:275, 1947.
10. Östling, G.: The Significance of the Speed of Injection for the Therapeutic Effect of K-Strophanthin, Acta med. Scandinav. **129**:77, 1947.
11. Bloomfield, R. A., Rapoport, B., Milnor, J. P., Long, W. K., Mebane, J. G., and Ellis, L. B.: The Effects of Cardiac Glycosides Upon the Dynamics of the Circulation in Heart Failure: I. Ouabain, J. Clin. Investigation **27**:588, 1948.
12. Ray, T., and LaDue, J. S.: The Intravenous Administration of Lanatoside C to Patients Taking Maintenance Doses of Folia Digitalis up to the Date of Hospitalization With Recurrent Congestive Heart Failure, Am. Heart J. **30**:335, 1945.
13. Wyckoff, J., and Goldring, W.: Intravenous Injection of Ouabain in Man, Arch. Int. Med. **39**:488, 1927.
14. Batterman, R. C., Rose, O. A., and DeGraff, A. C.: The Combined Use of Ouabain and Digitalis in the Treatment of Congestive Heart Failure, Am. Heart J. **20**:443, 1940.
15. Gold, H.: The Treatment of Cardiac Failure With Digitalis Glycosides, Mod. Concepts Cardiovas. Dis. **14**:11, 1945.
16. Wayne, E. J.: Clinical Observations on 2 Pure Glycosides of Digitalis, Digoxin, and Digitalinum Verum, Clin. Sc. **1**:63, 1933.
17. Fahr, G., and LaDue, J. S.: A Preliminary Investigation of the Therapeutic Value of Lanatoside C, Am. Heart J. **21**:133, 1941.
18. Gefter, W. L., and Leaman, W. G., Jr.: The Use of Ouabain in Rapid Cardiac Arrhythmias, Am. J. M. Sc. **205**:190, 1943.
19. Weisberger, A. S., and Feil, H.: Lanatoside C in the Treatment of Persistent Paroxysmal Auricular Tachycardia, Am. Heart J. **34**:871, 1947.
20. Barrow, J. G.: Treatment of Paroxysmal Supraventricular Tachycardia With Lanatoside C, Ann. Int. Med. **32**:116, 1950.
21. Enselberg, C. D.: The Esophageal Electrocardiogram in the Study of Atrial Activity and Cardiac Arrhythmias. In press.
22. Tandowsky, R. M., Oyster, J. M., and Silverglade, A.: The Combined Use of Lanatoside C and Quinidine Sulfate in the Abolition of Established Auricular Flutter, Am. Heart J. **32**:617, 1946.
23. Goldman, I. R., Blount, S. G., Jr., Friedlich, A. L., and Bing, R. J.: Electrocardiographic Observations During Cardiac Catheterization, Bull. Johns Hopkins Hosp. **86**:141, 1950.
24. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Seibel, R. E., and Evans, J. M.: Studies of Congenital Heart Disease: I. Technique of Venous Catheterization as a Diagnostic Procedure, J. Clin. Investigation **26**:547, 1947.
25. Batterman, R. C., and Gutner, L. B.: Hitherto Undescribed Neurological Manifestations of Digitalis Toxicity, Am. Heart J. **36**:582, 1948.

THE EFFECT OF RESPIRATION ON THE ARTERIAL PULSE IN LEFT VENTRICULAR FAILURE

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WITH THE TECHNICAL ASSISTANCE OF GRIFFITH BARLOW

THE effect of respiration on the arterial pulse has been the subject of extensive study. In normals[1,2] the changes in the arterial pressure during the respiratory cycle follow a typical course, with the mean pressure falling during inspiration and rising during expiration. In addition, there is evidence of changes in the stroke output from the left heart, resulting in an increased pulse pressure during expiration and a diminution during inspiration. These variations in pulse pressure result in corresponding variations in the strength of the arterial beat, with a large stroke volume giving a large beat and a small stroke output the reverse. The changes in the ballistocardiogram during the respiratory cycle are the reverse of the changes in the pressure and volume pulses, with increased amplitude during inspiration.[3]

It would not be unexpected that derangements of the circulatory system might alter the pattern of the respiratory variations of the pulse. Left ventricular failure, in particular, might be expected to give abnormal respiratory variations in the pulse, since here there is pronounced engorgement of the pulmonary bed. In a recent article McCann[4] cities evidence suggesting the active role of the pulmonary bed in regulation of the circulation. Brown and co-workers[5] report an abnormal respiratory variation in the ballistocardiogram in a certain group of patients with angina pectoris.

During the course of a survey of cardiac patients in the Los Angeles County General Hospital in which simultaneous recordings of the arterial pulse and respiration were made, it was noted that certain patients gave a pattern which did not conform with the normal, as the strongest arterial beats were found to occur during inspiration. The following report is a detailed study of this problem.

METHODS

Recordings of the arterial pulse were made from an ordinary blood pressure cuff placed around the upper arm of the subject. The pressure in the cuff

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was adjusted to a level of 10 to 20 mm. Hg below the subject's diastolic arterial pressure. An inelastic leather band was put over the cuff so that the system acted as a modified plethysmograph; any changes in volume of the arm caused corresponding small pressure changes in the cuff bag. These pressure variations were recorded by means of a strain gauge manometer* connected to an oscillograph. The rapid volume changes in the arm were largely the result of changes in the amount of blood in the large arteries in this region. The walls of these vessels acted like pressure tambours, so that the volume changes were proportional to the pressure changes of the blood within the vessels. This system was quite sensitive and slight changes in systolic pressure from beat to beat were readily indicated on the record by a rise in the peak of the pulse wave. Likewise, variations in the diastolic pressure of successive beats were quite accurately indicated by a change in the level of the wave trough. This technique, then, gave a measure of changes in the pulse pressure. In a given case, the relative amplitude of the recorded waves indicated the relative strengths of the successive beats. In the work here reported, we are concerned only with these changes in the amplitude of the pulse and not with any variation in mean arterial pressure.

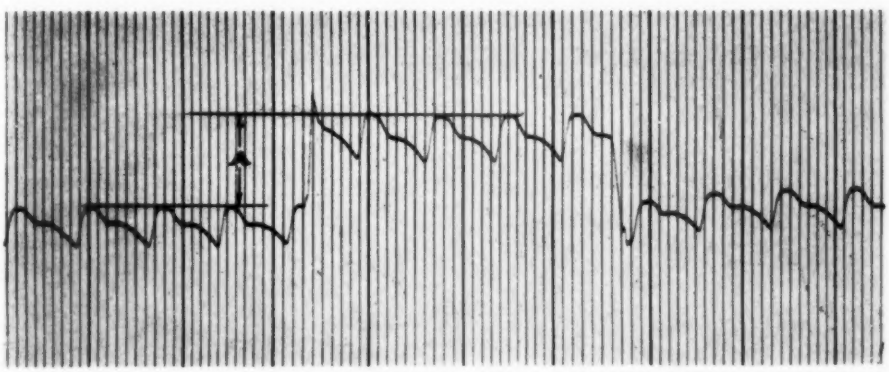


Fig. 1.—Volume calibration of cuff. 2 c.c. of air were injected at arrow.

A record of this type is illustrated in Fig. 1, which also shows the method of calibrating the volume change. In the middle of the record, 2 c.c. of air were added to the system and later removed. This gives an indication of the increase in volume of the arteries with each systole, in this case some 0.8 c.c.

A record of respiration was taken from a pneumograph encircling the chest, which activated a strain gauge manometer. This was recorded simultaneously with the pulse record.

PROCEDURE

Records were made, usually within twenty-four hours of entry to the hospital, on patients with a presumptive diagnosis of left ventricular failure. In addition, some records were obtained on patients in the wards who had been undergoing

*The strain gauge manometers were loaned by the Statham Laboratories of Beverly Hills, Calif.

treatment for varying periods of time. The diagnosis of left ventricular failure was based on the presence of dyspnea, orthopnea, cyanosis, râles throughout both lung fields, and physical or laboratory evidence of old or recent hypertensive or coronary artery heart disease.

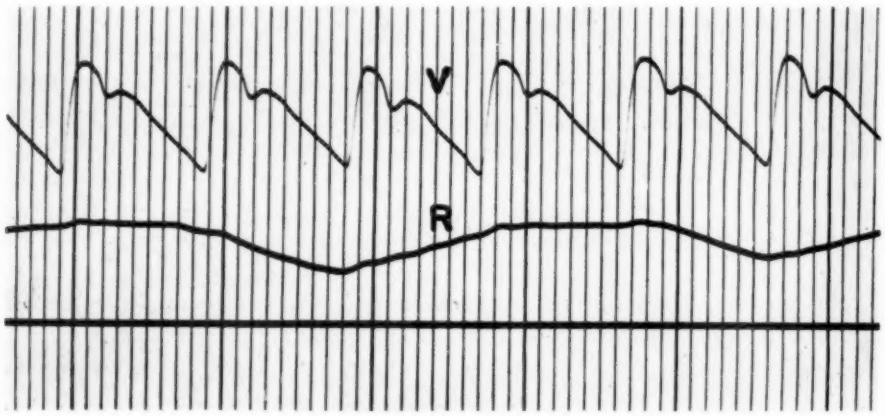


Fig. 2.—Subdiastolic pulse tracing in the control subject. See text for discussion. No. 1 control subject, Table I. V = volume pulse. In all diagrams, R = respiration, with inspiration down and expiration up. Time between heavy lines = 1 second.

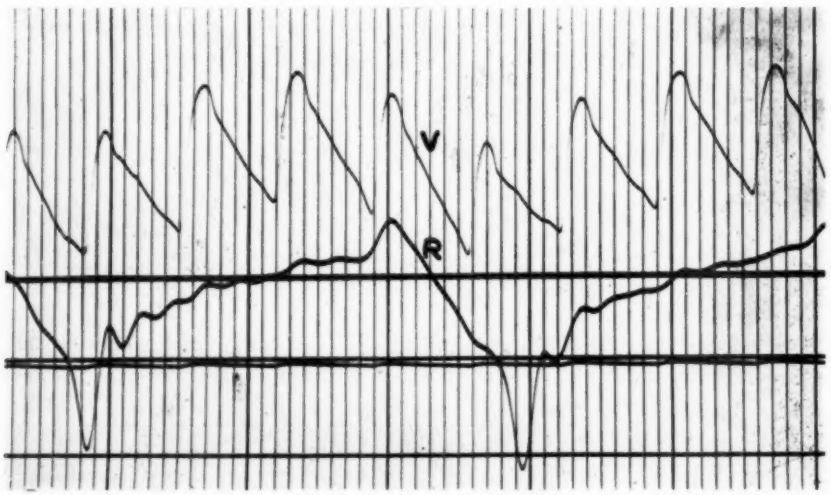


Fig. 3.—Subdiastolic pulse tracing in bronchial asthma. Patient No. 3, Table I, pulmonary disease.

As controls, records were obtained from patients with dyspnea due to obvious pulmonary disease, as bronchial asthma or bronchopneumonia. Finally, many records were examined on normal subjects.

RESULTS

The minimal changes occurring in the pressure pulse during each respiratory cycle in a control subject are shown in Fig. 2. Here is shown a slight increase

in the amplitude of the pressure pulse occurring during expiration with slight decrease during inspiration.

The changes associated with the dyspnea of bronchial asthma are seen in Fig. 3. Here there is an exaggeration of the normal pattern, with a fall in amplitude and drop in pressure and take-off during inspiration and an increase in amplitude during expiration.

In marked contrast is the respiratory change seen in left ventricular failure, illustrated in Figs. 4 and 5. In Fig. 4 a definite increase in the pulse pressure occurs during inspiration, with a fall during expiration. There is also a rise in diastolic pressure, as indicated by a rise in the diastolic trough.

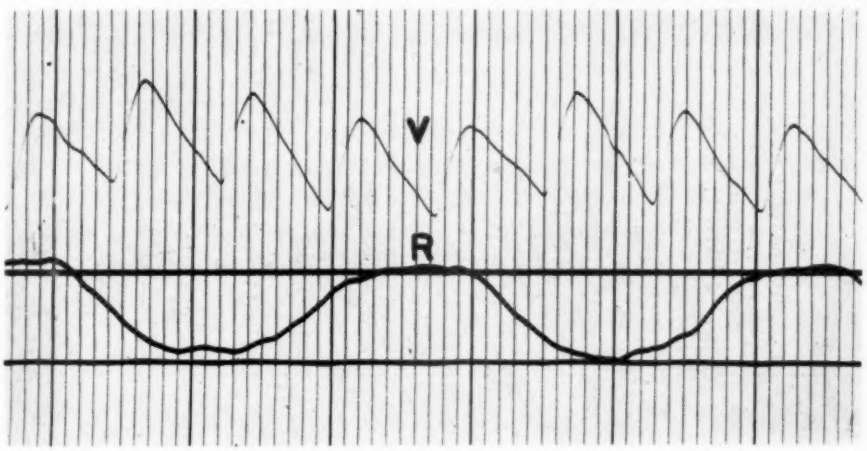


Fig. 4.—Subdiastolic pulse tracing in acute left ventricular failure. See text for discussion. Patient No. 1, Table I.

The same type of change is seen in Fig. 5,*A*, where a definite increase in amplitude is seen in inspiration, but with no shift in the take-off. Fig. 5,*B* from the same case shows the change from the anomalous to the normal pattern with recovery from left ventricular failure.

Records which showed any type of arrhythmia or marked alternation obviously could not be used in this study. After this selection there remained twenty-two patients with a presumptive diagnosis of left ventricular failure of varying degrees of severity. Of these, seven showed the anomalous pattern described above.

An analysis of these records is given in Table I with results from seven controls and seven patients with pulmonary disease for comparison. In the cardiac patients the greatest amplitude beat (pulse pressure) occurred usually 1 to 2 beats after the onset of inspiration, with the minimum amplitude 2 to 3 beats after the onset of expiration. The normal controls and the patients with pulmonary disease, in contrast, all showed the highest amplitude beat usually 2 to 3 beats after the onset of expiration, with the lowest amplitude beat either 1 or 2 beats after the onset of inspiration or early in expiration. Two of the cardiac patients (6 and 7 in Table I) were studied during failure and after re-

TABLE I. EFFECT OF RESPIRATION ON PULSE VOLUME AT THE SUBDIASTOLIC LEVEL

SUBJECT NO., AGE, AND SEX	PULSE RATE (PER MINUTE)	RESPIRATORY RATE (PER MINUTE)	CYCLE INSPIRATION EXPIRATION (SECONDS)	HIGHEST AMPLITUDE BEAT (BEAT AFTER ONSET OF INSPIRATION [I] OR EXPIRATION [E])	LOWEST AMPLITUDE BEAT (BEAT AFTER ONSET OF INSPIRATION [I] OR EXPIRATION [E])	DIAGNOSIS
Left Ventricular Failure						
1 76 M	96	15	1.26 I 2.65 E	Second I (0.88 sec.)*	Second E (0.89 sec.)	Myocardial infarction
2 79 M	94	21	1.3 I 1.6 E	First I (0.6 sec.)	Second E (1.4 sec.)	Hypertensive heart disease in failure
3 71 M	94	46	0.4 I 0.9 E	First I (0.2 sec.)	First E (0.2 sec.)	Myocardial infarction (?); hypertensive heart disease in failure
4 63 F	84	27	0.9 I 1.3 E	First I (0.57 sec.)	First E (0.4 sec.)	Hypertensive heart disease in failure
5 51 M	125	23	0.73 I 1.87 E	First I (0.15 sec.) First E (0.141 sec.)	Second E (0.68 sec.)	Myocardial infarction (?); hypertensive heart disease in failure
6 73 M	102	20	1.00 I 2.00 E	First I (0.4 sec.)	Third E (1.3 sec.)	Myocardial infarction (?); hypertensive heart disease in failure
Recovery	78	15	1.6 I 2.42 E	Fourth E (2.4 sec.)	Second E (1.19 sec.)	
7 64 M	77	24	1.45 I 1.01 E	Second I (0.93 sec.)	Second E (1.0 sec.)	Hypertensive heart disease in failure
Recovery	84	20	1.3 I 1.7 E	First E (0.5 sec.)	First and second I (0.2 and 0.9 sec.)	

Pulmonary Disease

59	1 M	108	27	1.1 I 1.1 E	Third E (1.1 sec.)	First I (0.5 sec.) Second E (0.54 sec.)	Asthma; bronchopneumonia; emphysema; bronchiectasis
45	2 M	132	31	0.78 I 1.17 E	Second E (0.53 sec.)	First I (0.37 sec.)	Pneumonia
65	3 M	90	19	0.94 I 2.2 E	Second E (1.32 sec.)	First I (0.5 sec.)	Asthma; emphysema
58	4 M	90	24	0.95 I 1.55 E	First E (0.4 sec.)	Second E (0.7 sec.)	Asthma
73	5 M	78	28	0.82 I 1.35 E	Second E (1.22 sec.)	First E (0.47 sec.)	Silicosis; emphysema; cor pulmonale
70	6 M	96	30	0.5 I 1.5 E	First E (0.47 sec.) Second E (1.2 sec.)	First I (0.22 sec.)	Emphysema; cor pulmonale
59	7 M	90	22	1.05 I 1.65 E	Second E (0.78 sec.)	First I (0.45 sec.)	Bronchopneumonia

Control Subjects

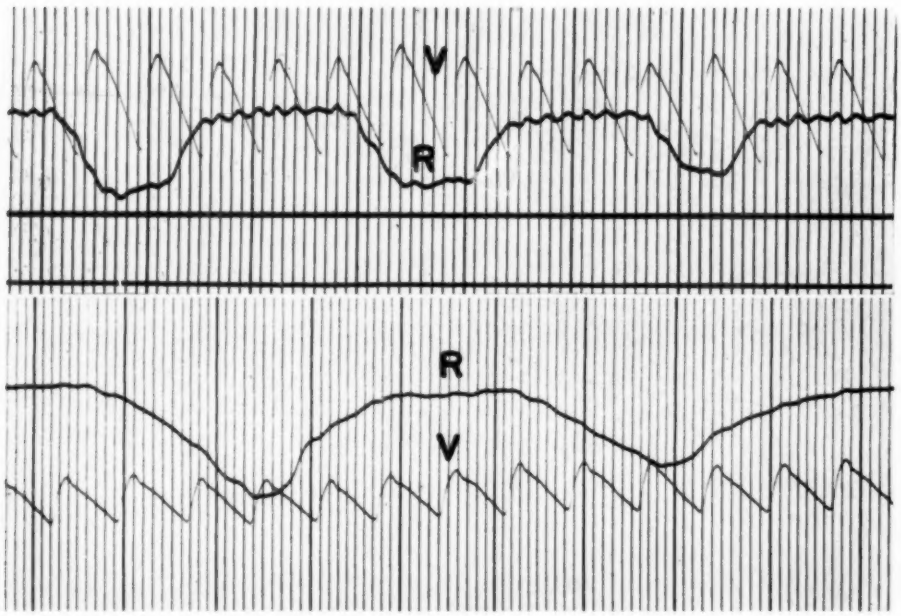
24	1 M	60	21	0.85 I 2.05 E	Second E (0.87 sec.)	First I (0.74 sec.)	Normal
30	2 M	84	14	1.86 I 2.4 E	Third E (1.5 sec.)	First E (0.1 sec.)	Normal
43	3 F	72	23	1.0 I 1.6 E	Second E (1.25 sec.)	First E (0.4 sec.)	Normal
29	4 M	72	18	1.4 I 2.0 E	Second E (1.1 sec.)	Second I (1.07 sec.)	Normal
25	5 M	60	11	2.26 I 3.04 E	Second E (1.7 sec.)	Second I (1.8 sec.)	Normal
21	6 M	66	20	1.07 I 1.9 E	Second E (1.2 sec.)	First E (0.05 sec.)	Normal
31	7 M	78	14	1.99 I 2.3 E	Second E (1.29 sec.)	Second I (1.22 sec.)	Normal

*The time given in parenthesis refers to time after onset of either inspiration or expiration to beginning of beat indicated.

covery, and both showed a return to the normal pulse pattern with clinical improvement of the heart failure.

In Fig. 6 there is depicted graphically the position in the respiratory cycle of the largest beat and in Fig. 7 of the smallest beats. The positions are plotted as fractions of the two phases of respiration and show the striking difference between the cardiac patients and the controls.

A.



B.

Fig. 5.—Subdiastolic pulse tracing in acute left ventricular failure. See text for discussion. Patient No. 6, Table I. *A*, in failure; *B*, recovery from failure.

DISCUSSION

No conclusions should be made as to the incidence of this anomaly in acute cardiac failure. The patients examined in this series were not always in the same stage of failure. In the early part of the study some records were taken on patients who were obviously well on the way to recovery from acute left heart failure. Later, it became apparent that only patients with severe failure showed the anomalous pattern. Three of the seven patients with this pattern died within seventy-two hours of entry to the hospital. Also in this connection, it is noteworthy that, in the two patients from whom records were obtained after recovery, the pulse pattern reverted to normal. It is likely, therefore, that the incidence of this anomaly would be higher than 7 in 22 if the cases considered were limited to severe cardiac failures.

In considering the mechanisms responsible for this change, dyspnea can be ruled out, since the pulse abnormality was not shown by the patients with severe dyspnea due to lung disease.

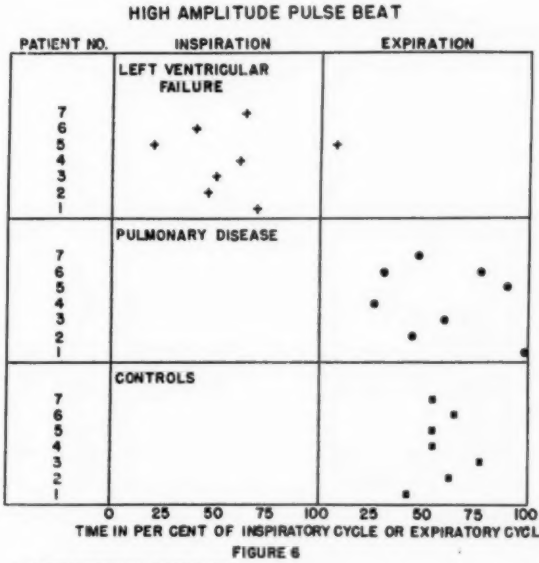


FIGURE 6

✦ LEFT VENTRICULAR FAILURE
● PULMONARY DISEASE
▪ CONTROLS
NUMBERS REFER TO SUBJECT NUMBER IN TABLE I

Fig. 6.—Showing the position in the respiratory cycle when the largest beat occurs. In each case the time of occurrence of the large beat is indicated by its position in the particular respiratory phase (inspiration or expiration) in which the beat occurred.

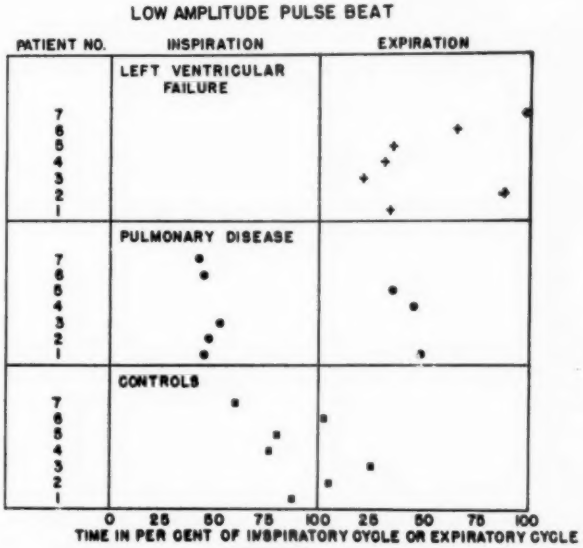


FIGURE 7

✦ LEFT VENTRICULAR FAILURE
● PULMONARY DISEASE
▪ CONTROLS
NUMBERS REFER TO SUBJECT NUMBER IN TABLE I

Fig. 7.—Showing the position in the respiratory cycle when the smallest beat occurs. In each case the time of occurrence of the small beat is indicated by its position in the particular respiratory phase (inspiration or expiration) in which the beat occurred.

The change may be associated with congestion of the pulmonary vessels. How can this condition change the respiratory response? In the normal the changes in the pulse caused by breathing are due chiefly to two mechanisms. The first is the direct effect of increased intrathoracic pressure on the heart and upper aorta. Since these are within the thorax, the variations in intrathoracic pressure are transmitted through their walls to the blood within them. These pressure changes result in changes in the mean arterial pressure and have little effect on the pulse pressure.[2] The second mechanism is the aspiratory action of lowered intrathoracic pressure during inspiration. This increases the flow of blood from the systemic veins into the right heart. This increase is transmitted to the left heart in 2 or 3 seconds, by which time usually the expiratory phase of the respiratory cycle has commenced.[6]

In normals the decreased intrathoracic pressure of inspiration does not directly increase the filling of the left ventricle, since both the pulmonary veins and the left ventricle are subjected to the same changes in intrathoracic pressure. The walls of the veins are only slightly stretched, since the pulmonary venous pressure is a little above intrathoracic pressure; hence, any change in the latter is readily transmitted to the former. In other words, the pulmonary veins are similar to a thin-walled, lax rubber bag, partially filled with liquid. It is obvious that any pressure change in the atmosphere around the bag will be transmitted to within the bag. In left heart failure, on the other hand, the pulmonary veins are markedly distended by the pressure of blood within them. The tension on the vein walls is then so high that they can stretch little with any further increase in tension. A decrease in intrathoracic pressure in this case would cause little if any decrease in pressure in the veins,* although it might be communicated to the left ventricle during diastole if its walls are not overstretched at this time. Inspiration, because it decreases the left ventricular pressure, then would increase the gradient of pressure between the pulmonary veins and the left ventricle and, hence, increase the ventricular filling.

Preliminary studies[7] have shown that this anomalous effect of respiration on the pulse can be simulated in normals by having them breathe to and from pressure some 20 to 30 mm. Hg below the ambient pressure. This maneuver increases the amount of blood in the lungs. This effect then is most likely to be related to engorgement of the pulmonary vessels.

Another possibility is that the changed state of the pulmonary bed may be responsible for this phenomenon, although this must be speculative since the effect of expansion and collapse of the lungs on the capacity of the pulmonary bed is controversial. It has been generally assumed that the capacity of the pulmonary bed increases on expansion (inspiration). However, recent work by Visscher[8] casts doubt on this and supports the view that the capacity of the pulmonary bed is increased in expiration. This would mean that the lung would tend to deliver more blood to the left heart during inspiration, and this effect would be accentuated if the pulmonary vessels were distended by passive congestion.

*A simple analogy to this situation is a football blown up fully. This could be put in a vacuum without changing appreciably the pressure of the air within it.

The possibility that changes in intrathoracic pressure or diastolic volume of the left ventricle may play a role in this phenomenon cannot be entirely excluded. In heart failure the cardiac output is usually low, and there is inability to increase to any degree the output in most instances after exercise.[9] A decrease in peripheral resistance, however, may increase the cardiac output in congestive failure, as demonstrated by the work of Ferrer and associates[10] with quinidine. The decrease in pressure within the thoracic aorta, which occurs during inspiration, could serve in the same fashion. The effect of decreased intrathoracic pressure would not be as marked on a dilated left ventricle. Therefore, an increase in left ventricular output could occur under these circumstances due to decreased peripheral resistance. This could increase the pulse volume in the extremities to such a degree as to overbalance the transmitted decrease of intrathoracic pressure which occurs during inspiration.

SUMMARY

An anomalous effect of respiration on the arterial pulse has been found in several patients with severe left heart failure. In contrast to the behavior of the pulse in normals in which the pulse beat becomes stronger in expiration, in these cases the strong beats occurred in inspiration. In two of the cardiac patients the pattern reverted to normal with clinical improvement.

REFERENCES

1. Wiggers, Carl J.: The Effects of Respiration on Blood Pressure, in Physiology in Health and Disease, ed. 5, Philadelphia, 1949, Lea & Febiger, p. 612.
2. Hamilton, W. F., Woodbury, R. A., and Harper, H. T.: Physiologic Relationships Between Intrathoracic, Intraspinal and Arterial Pressures, J. A. M. A. **107**:853, 1936.
3. Starr, Isaac, and Friedland, Carl: On the Cause of the Respiratory Variation of the Ballistocardiogram, With a Note on Sinus Arrhythmia, J. Clin. Investigation **25**:53, 1946.
4. McCann, William S.: Some Neglected Aspects of Cardiology: Circulatory Function of the Respiration, Am. J. Med. **8**:62, 1950.
5. Brown, Herbert R., Jr., Hoffman, Marvin J., and de Lalla, Vincent, Jr.: Ballistocardiographic Findings in Patients With Symptoms of Angina Pectoris, Circulation **1**:132, 1950.
6. Lauson, H. D., Bloomfield, R. A., and Cournand, A.: Influence of the Respiration on the Circulation in Man, Am. J. Med. **1**:315, 1946.
7. Drury, D. R., and Meehan, John P.: Unpublished data.
8. Visscher, Maurice B.: The Capacity Changes in the Pulmonary Vascular Bed With the Respiratory Cycle, Federation Proc. **7**:128, 1948.
9. Hickam, John B., and Cargiel, Walter H.: Effect of Exercise on Cardiac Output and Pulmonary Arterial Pressure in Normal Persons and in Patients with Cardiovascular Disease and Pulmonary Emphysema, J. Clin. Investigation **27**:10, 1948.
10. Ferrer, M., Irené, Harvey, Réjane, M., Werkö, Lars, Dresdale, David T., Cournand, André, and Richards, Dickinson W., Jr.: Some Effects of Quinidine Sulfate on the Heart and Circulation in Man, Am. Heart J. **36**:816, 1948.

ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH ALLERGIC REACTIONS TO PENICILLIN

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ANATOMIC and functional cardiac changes occurring in the presence of allergic reactions have been reported by various investigators.[1-5] Longcope,[1] in 1915, demonstrated interstitial myocarditis, as well as focal areas of degeneration in the heart muscle, kidney, and liver, following injection of foreign proteins into sensitized rabbits, and Boughton,[2] in 1917, found lesions of the smaller arteries of the liver, kidney, spleen, and heart, following injection of foreign protein into sensitized guinea pigs.

Clark and Kaplan[6] have reported two instances of death following serum sickness in which autopsy disclosed interstitial myocarditis, valvulitis, and vascular lesions of the periarteritis nodosa type. McManus and Lawlor[7] reported one case of myocardial infarction occurring during serum sickness and cited three others from the literature. De Lavergne, Morel, and Jochum[8] reported the occurrence of transitory Stokes-Adams syndrome, and Weille-Halle and Levy,[9] the development of extrasystoles and muffled first sound in the course of serum sickness. Wadsworth and Brown[10] described a case of serum carditis in an 11-year-old boy and Fox and Messeloff,[11] transient electrocardiographic changes in a patient with serum sickness following tetanus antitoxin.

We have observed transient electrocardiographic changes in three patients who developed severe allergic reactions in the course of penicillin therapy.

CASE REPORTS

CASE 1.—B. V. B., a 27-year-old white man, was admitted to Wadsworth General Hospital July 22, 1948, with complaints of fever and painful swollen joints of four days duration.

He received penicillin in oil three weeks previously because of pleuritic pain, fever, and cough. He received a second injection four or five days later and a third injection on the day before admission. Three days prior to admission, a migratory polyarthritis appeared, involving in rapid succession his right ankle, left ankle, right knee, both wrists, both elbows, and finally the left shoulder. Four hours after the last injection, a pruritic rash appeared about his forehead and neck, and the left eye became swollen.

The temperature on admission was 98.6° F., pulse 84 per minute, and the blood pressure 120 mm. Hg systolic and 80 mm. Hg diastolic. Many urticarial lesions were present about the forehead, neck, and right lateral chest. There was swelling, tenderness, and limitation of motion

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of the left wrist, and increased warmth of the left shoulder. The heart was not enlarged, and there were no murmurs. The remainder of the physical examination was negative.

The red blood count was 5,200,000; white blood count 10,450 with 88 per cent neutrophils, 11 per cent lymphocytes, and 1 per cent eosinophils. Urinalysis was negative. The sedimentation rate was 20 mm. per hour. The Kahn reaction was negative. Chest roentgenogram was normal. An electrocardiogram taken on July 23, 1948 showed inversion of the T waves in all the limb leads and in V_5 (Fig. 1).

Because of a past history of rheumatic fever, the patient was given 8.0 Gm. of aspirin during the first hospital day. He was at bed rest and received 200 mg. of Pyribenzamine with no relief of symptoms. The arthralgias became more severe. On the second day, he received 12.0 Gm. of aspirin. His temperature rose to 102° F., and he developed generalized urticaria with marked pruritus. On the third day, aspirin was discontinued. Procaine hydrochloride, 1.0 Gm. in 500 c.c. of normal saline, was given slowly by vein. The soreness and stiffness of the joints gradually subsided, the pruritus abated, and the temperature fell by lysis over a period of four days. Electrocardiograms taken on July 26, 28, and on Aug. 2, 1948, showed a rapid return to a normal pattern (Fig. 1). The sedimentation rate on July 28, 1948 was 3 mm. per hour. The patient was discharged afebrile and asymptomatic on Aug. 6, 1948.

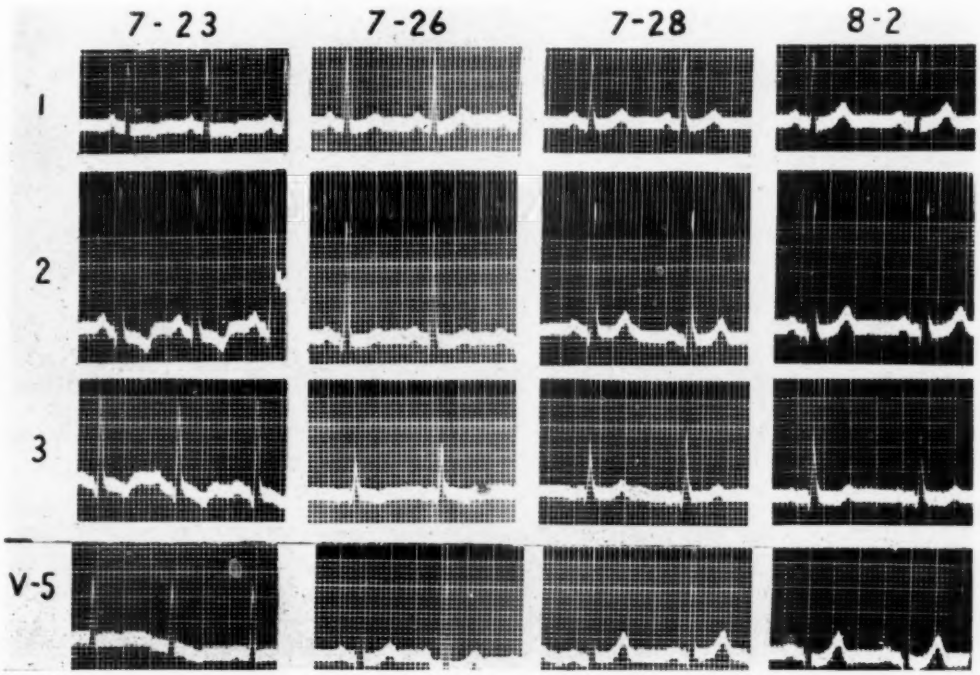

Fig. 1.—Case 1. T waves inverted in Leads I, II, III, and V_5. Return to normal in five days.

Case 2.—J. E. K., a 24-year-old white man, was admitted to Wadsworth General Hospital July 27, 1948, with an urticarial skin rash, periorbital swelling, soreness of the mouth, and joint swelling and tenderness of two days duration.

The patient had noted a clear penile discharge on July 15, 1948. For this he was given intramuscular injections of penicillin in oil daily for six days. The allergic reaction began four days after the last injection. A series of injections of penicillin had been given in 1945 without reaction.

The temperature on admission was 100.4° F., the pulse rate 84 per minute, and the blood pressure 125 mm. Hg systolic and 70 mm. Hg diastolic. There were giant urticarial lesions covering the body, particularly on the extremities, including the palms of the hands, the soles of the

feet, and on the dorsal surface of the trunk. There was periorbital edema. The lips were puffy and tender, and the gums were edematous and sore. The wrists were swollen and tender. There was a Grade 2 systolic murmur at the cardiac apex transmitted upward to the pulmonic area, but examination of the heart was otherwise negative. There was a slight urethral discharge. The remainder of the physical examination was negative.

The red blood count was 4,950,000; white blood count 7,700 with 77 per cent neutrophils, 20 per cent lymphocytes, and 1 per cent each of monocytes, eosinophils, and basophils. Urinalysis was negative. The sedimentation rate was 12 mm. per hour. The Kahn reaction was negative. Two urethral smears did not reveal any Gram-negative diplococci. Chest roentgenogram was normal. Serial electrocardiograms showed transient T-wave changes (Fig. 2).

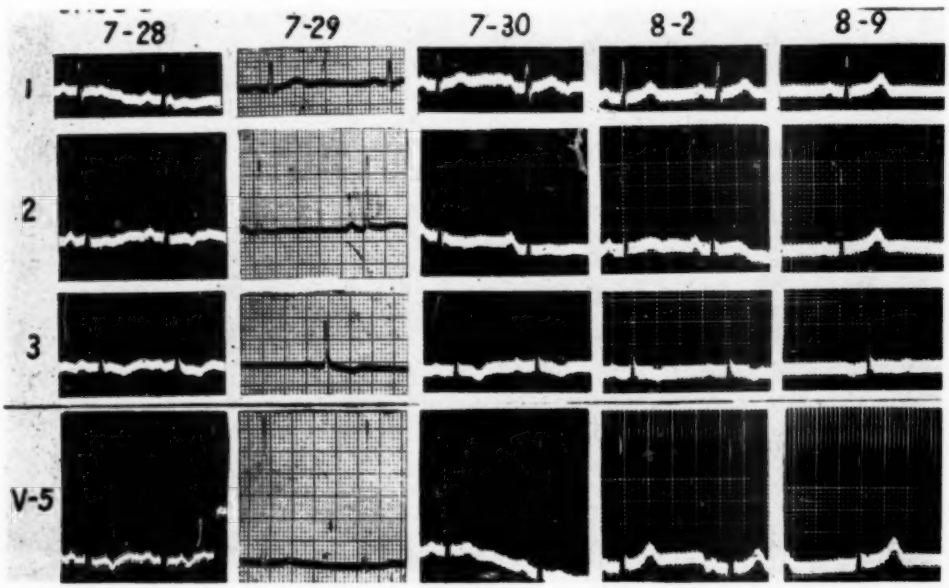

Fig. 2.—Case 2. T_1 isoelectric; T_2 and T_3 inverted; T waves inverted in V_4, V_5, and V_6. (V_5 is shown as a representative lead.) Return to normal in approximately one week.

The patient had no relief from bed rest, Pyribenzamine 100 mg. every three hours, phenobarbital 60 mg. three times a day, and calamine lotion with 1 per cent phenol locally. The temperature rose to 101.6° F. on the day of admission. Procaine hydrochloride, 1.0 Gm. in 500 c.c. of normal saline, administered slowly by vein, gave marked symptomatic relief. The temperature returned to normal; periorbital edema, tenderness of gums, urticaria, and arthralgia subsided. On the third day, edema of the gums and labial herpes were the only signs present. On the fourth day, the patient complained of pruritus of the legs. Erythema without urticaria was present. On the third and fourth days of hospitalization, Adrenalin in oil was given intramuscularly. By the fifth day he was asymptomatic and remained so until discharge.

Case 3.—I. J. S., a 50-year-old white male physician, was admitted to Wadsworth General Hospital Oct. 4, 1948, with complaints of fever, weakness, generalized urticaria, and painful swollen joints of five days duration.

Because of an infected tooth, he was given intramuscular injections of penicillin in oil and beeswax daily for four days, beginning September 16. Ten days after the last injection, he noted the onset of symptoms. Past history revealed an urticarial response to Nembutal in 1941 and the presence of chronic allergic rhinitis.

The temperature on admission was 100.6° F., pulse 96 per minute, and the blood pressure 100 mm. Hg systolic and 60 mm. Hg diastolic. Numerous urticarial lesions were present. There was

tenderness and swelling of many interphalangeal joints. The heart was not enlarged, and there were no murmurs. The remainder of the physical examination was negative.

The red blood count was 5,100,000; white blood count 5,900 with 82 per cent neutrophils, 16 per cent lymphocytes, and 2 per cent eosinophils. Urinalysis was negative. The sedimentation rate was 17 mm. per hour. The Kahn reaction was negative. Chest roentgenogram was normal. Electrocardiograms showed transient T-wave inversion (Fig. 3).

The patient was placed at bed rest and given 500 mg. of Pyribenzamine daily by mouth, and 10 c.c. of calcium gluconate twice daily by vein. He became afebrile and asymptomatic on the third hospital day and was discharged on Oct. 11, 1948.

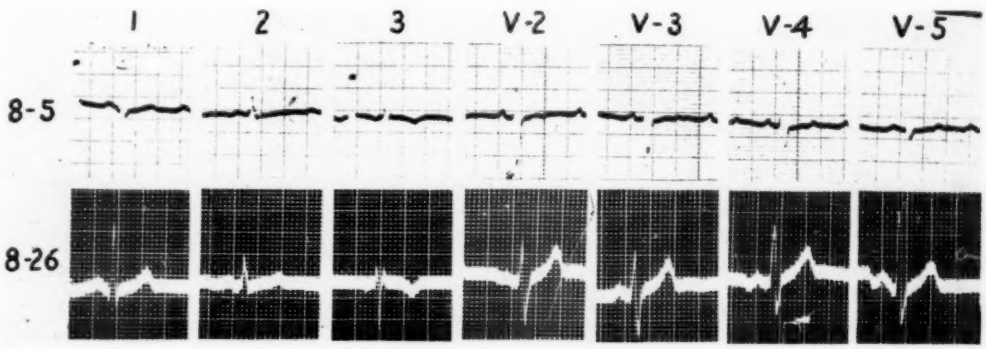

Fig. 3.—Case 3. Low upright T_1; isoelectric T_2; inverted T in V_2; diphasic T in V_3 and V_4; low upright T in V_5. Electrocardiogram taken three weeks later was normal.

DISCUSSION

All three patients were acutely ill with moderate temperature elevation, generalized urticaria, and swollen painful joints. These allergic manifestations were thought to result from penicillin sensitivity. There were no complaints referable to the cardiovascular system. The initial electrocardiograms were taken at the height of the allergic reaction. The electrocardiographic changes observed were similar to those previously described as attributable to serum carditis or anoxia.[11,12] Transient pericarditis, as part of a generalized serous membrane allergic response, may produce similar changes.

Two of the patients received penicillin in oil, and one patient received penicillin in oil and beeswax. The part played by the menstruum in these allergic reactions remains undetermined. However, it has been amply demonstrated clinically that penicillin alone can produce allergic reactions of this severity.

Twenty-five additional patients with mild allergic reactions during penicillin therapy were studied and electrocardiographic abnormalities were not found. This suggests that electrocardiographic changes occur only with the most severe penicillin reactions.

SUMMARY

Electrocardiographic changes, represented mainly by transient T-wave inversion, occurred in three patients who developed severe allergic reactions in the course of penicillin therapy.

These changes resemble those previously reported in other allergic reactions.

REFERENCES

1. Longcope, W. T.: The Effect of Repeated Injections of Foreign Protein on the Heart Muscle, Arch. Int. Med. **15**:1079, 1915.
2. Boughton, T. Harris.: Studies in Protein Intoxication, J. Immunol. **2**:50, 1917.
3. Rich, A. R., and Gregory, J. E.: Experimental Evidence That Lesions With Basic Characteristics of Rheumatic Carditis Can Result From Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **73**:239-264, 1943.
4. Fox, R., and Jones, L.: Vascular Pathology in Rabbits Following Administration of Foreign Protein, Proc. Soc. Exper. Biol. & Med. **55**:294, 1944.
5. Kyser, F. A., McCarter, J. C., and Stengle, J.: Effect of Antihistaminic Drugs Upon Serum-induced Myocarditis in Rabbits, J. Lab. & Clin. Med. **32**:379-386, 1947.
6. Clark, E., and Kaplan, B. I.: Endocardial Arterial and Other Mesenchymal Alterations Associated With Serum Disease in Man, Arch. Path. **24**:458-475, 1937.
7. McManus, John F., and Lawlor, James J.: Myocardial Infarction Following the Administration of Tetanus Antitoxin, New England J. Med. **242**:17-19, 1950.
8. De Lavergne, Morel, and Jochmann.: Syndrome de Stokes-Adams transitoire, servenu en même temps que des accidents sériques, à la convalescence d'un érysipèle de la face, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1314-1318, 1927.
9. Weille-Halle, B., and Levy, P.: Serum Sickness, Bull. et mém. Soc. méd. d. hôp. de Paris **45**:260, 1921.
10. Wadsworth, G. H., and Brown, C. H.: Serum Reaction Complicated by Acute Carditis, J. Pediat. **17**:801-805, 1940.
11. Fox, T. T., and Messeloff, C. R.: Electrocardiographic Changes in Case of Serum Sickness Due to Tetanus Antitoxin, New York State J. Med. **42**:152-154, 1942.
12. Castberg, Thomas, and Schwartz, Michael: Changes in the Electrocardiogram During Allergic Shock, Acta Med. Scandinav. **126**:459-471, 1947.

Clinical Reports

ACUTE MYOCARDIAL INFARCTION DURING A PROLONGED ALLERGIC REACTION TO PENICILLIN

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WHEN considering the etiology in any given case of acute myocardial infarction, one does not usually give serious consideration to allergy. The literature of recent years abounds with reports of allergic reactions and serum sickness following parenteral therapy, and there is a growing cognizance that these reactions may produce injury to the heart[1-11] and other vital organs.[12,13,14]

Four cases of myocardial infarction following administration of antitetanic serum have been reported.[1,8,10,15] We wish to report a case of acute myocardial infarction which occurred during a prolonged allergic reaction to penicillin.

CASE REPORT

A 49-year-old white man was admitted to Loretto Hospital on May 15, 1950, complaining of substernal oppressive pain with vomiting, diarrhea, and weakness for one day. He stated that he had been perfectly well until Jan. 10, 1950, when he was treated in another institution for a severe hand injury. At that time, he was given 1,500 units of antitetanic serum and 300,000 units of penicillin in oil daily for four days. Four weeks after treatment, he developed urticaria which had been almost continuous for 125 days.

A dermatologist made a diagnosis of delayed reaction to penicillin and assured the patient that the skin lesions were harmless, but might be recurrent for a period of months. The patient's past and family history were entirely noncontributory. He denied hypertension, kidney disease, heart disease, or previous allergy.

Physical examination revealed a well-developed, well-nourished, white man who was acutely ill and apprehensive. There was mild cyanosis of the lips. The blood pressure was 108/78 mm. Hg bilaterally; the pulse rate was 100 to 110 with occasional premature systoles. There were raised areas of erythema over the upper thighs, buttocks, and legs. The heart tones were of decreased intensity. The fundi were normal.

The Kahn reaction was negative. Blood counts were normal, and there were no eosinophiles. There was albuminuria grade 3 plus on one occasion, but the urine was otherwise repeatedly normal. Lee-White coagulation time on May 15, 1950 was five minutes and prothrombin time was 100 per cent. Blood sugar was 99 mg. per cent fasting and 133 mg. per cent two and one-half hours after a meal. Blood cholesterol was 182 mg. per cent. The electrocardiogram on May 16, 1950 revealed inversion of T waves in Leads I and V_1 to V_5 with elevated convex ST sectors. There were Q waves in Lead I, Leads V_1 to V_3 and also in aV_L. Classical serial changes were present in subsequent examinations and were considered diagnostic of large anteroseptal infarction.

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The patient was treated with Dicumarol, papaverine, morphine, and Benadryl. The urticaria was mildly recurrent until July 15, 1950, when it disappeared.

DISCUSSION

This case of myocardial infarction occurred during a prolonged hypersensitivity reaction to penicillin. There was no evidence of the common predisposing causes of coronary occlusion such as hypertension, diabetes, hypercholesterolemia, or peripheral arteriosclerosis, and, hence, one must consider hypersensitivity to penicillin as its cause. Morphologic proof for such occurrences in animals and man has been offered by Rich[4,9] and other investigators.[2,14] These changes are usually mediated through periarteritis or allied changes.[18]

Periarteritis nodosa is generally or widely believed to be the result of an allergic vascular reaction[16] and is a known but rare cause of coronary occlusion.[17] The infarction in this patient seems to have had a definite relation to allergy, and the mechanism may well have been on the basis of periarteritis.

While our patient had received both tetanus antitoxin and penicillin, we feel justified in assuming that the allergic response in this case was due to penicillin because of its long delayed onset and protracted course. There have been no reported cases of myocardial infarction during allergic reactions to penicillin. However, pericardial friction rubs[11] and carditis[12] have been observed in association with skin sensitivity reactions to penicillin.

It has been suggested that a greater number of coronary accidents would be found in such cases if the patients were more carefully followed,[10] and especially if the possibility of such complications were borne in mind.

SUMMARY

A case of prolonged sensitivity reaction to penicillin complicated by acute myocardial infarction is presented. Since the patient recovered, one can only speculate as to the mechanism involved.

REFERENCES

1. Queries and Minor Notes: Tetanus Antitoxin or Coronary Thrombosis as a Cause of Death, J. A. M. A. **111**:1316, 1938.
2. Clark, E.: Serum Carditis: Morphologic Cardiac Alterations in Man Associated With Serum Disease, J. A. M. A. **110**:1098, 1938.
3. Wadsworth, G. M., and Brown, C. H.: Serum Reaction Complicated by Acute Carditis, J. Pediat. **17**:801, 1940.
4. Rich, A. R., and Gregory, J. E.: Experimental Evidence That Lesions With Basic Characteristics of Rheumatic Carditis Can Result From Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **73**:239, 1943.
5. Senerf, D., and Boyd, L. J.: Cardiovascular Diseases, Philadelphia, 1947, J. B. Lippincott Company, p. 147.
6. Cooke, R. A.: Allergy in Theory and Practice, Philadelphia, 1947, W. B. Saunders Company, p. 375.
7. Fox, T. P., and Messeloff, C. R.: Electrocardiographic Changes in a Case of Serum Sickness Due to Tetanus Antitoxin, New York State J. Med. **42**:152, 1942.
8. Boas, E. P.: Some Immediate Causes of Cardiac Infarction, AM. HEART J. **23**:1, 1942.
9. Rich, A. R., and Gregory, J. E.: Experimental Anaphylactic Lesions of Coronary Arteries of "Sclerotic Type," Commonly Associated With Rheumatic Fever and Disseminated Lupus Erythematosis, Bull. Johns Hopkins Hosp. **81**:312, 1947.
10. McManus, J. F., and Lawlor, J. J.: Myocardial Infarction Following the Administration of Tetanus Antitoxin, New England J. Med. **242**:17, 1950.

11. Master, A. M., Jaffe, H. L., and Dorrance, W. R.: The Treatment of Heart Failure: Digitalis and Mercurial Intoxication, Penicillin, Dicumarol, Major Surgery, New York State J. Med. **50**:553-559, 1950.
12. Felder, S. L., and Felder, L.: Unusual Reaction to Penicillin, J. A. M. A. **143**:361, 1950.
13. Urback, E., and Gottlieb, F. M.: Allergy, ed. 2, New York, 1946, Grune & Stratton, Inc., p. 828.
14. Clark, E., and Kaplan, B. I.: Endocardial, Arterial and Other Mesenchymal Alterations Associated With Serum Disease in Man, Arch. Path. **24**:458, 1937.
15. Mathieu, L., Hadot, S., and Hadot, E.: Infarctus du myocarde et angor consecutifs à des accidents sérothérapiques, Arch. d. mal. du coeur **40**:328, 1947.
16. Heck, F. J.: Introduction to Symposium on Periarteritis Nodosa, Proc. Staff Meet., Mayo Clin. **24**:17, 1949.
17. Cecil, R. L.: Textbook of Medicine, Philadelphia, 1948, W. B. Saunders Company, p. 1217.
18. Griffith, G. C., and Huntington, R. W., Jr.: Sudden Death in Rheumatic Fever, Ann. Int. Med. **25**:283-292, 1946.

PARCHMENT HEART (OSLER)

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IN REVISING the sixth edition (1905) of his textbook,[2] Osler introduced the following brief paragraph in the chapter on dilatation of the heart: "Dilatation may be chronic, in which case it is associated with hypertrophy. Not always however; there is an extraordinary heart in the McGill College Museum showing a parchment-like thinning of the walls with uniform dilatation of all the chambers; in places in the right auricle and ventricle, only the epicardium remains." This heart is now part of the Osler collection of specimens arranged by the late Dr. Maude E. Abbott during her curatorship of the museum. A recent thorough search of the museum records revealed no clue to the autopsy report concerned with this heart which represents a very rare abnormality, for no reference to such myocardial dilatation could be found in the ancient, the old, or the recent medical literature.

As this heart is viewed, suspended in liquid, it resembles a large cyst, and its walls quiver when the jar is tapped or shaken gently. Indeed, only the demonstration of the four heart valves, the aorta and pulmonary artery, and the four cavities removes the initial doubt as to the specimen being that of a heart (Fig. 1). It now weighs 168 grams. The epicardium is thin. The cavities are greatly dilated, the right more than the left. As Osler pointed out, the walls of the auricles and ventricles are of "parchment-like" thinness. The interventricular septum is the thickest portion and at its maximum measures 5 mm. If hypertrophy had developed commensurate with this degree of dilatation, the heart should have weighed about 1,000 grams. Judging by the two plaques of arteriosclerosis on the first portion of the aorta, it would seem that the person was in his forties or perhaps fifties. The coronary veins reveal no abnormalities. The coronary arteries are patent, quite large, and free from arteriosclerosis. Therefore, the condition of the myocardium cannot be attributed to impairment in coronary circulation. The aorta and pulmonary artery are within the normal range in size, but somewhat thinner than expected in an adult. All valves are free from disease or congenital abnormality and seem adequate in size and shape to have performed their functions efficiently. The histological study* of the

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*I am greatly indebted to Professor Lyman G. Duff for his kindness in making studies of the histological slides and for permitting me to report this heart, which is now in his care in the Department of Pathology, McGill University.

myocardium of the ventricular walls and of the interventricular septum revealed no satisfactory clue to the disease. The architecture of the myocardium seemed to be normal; the details of muscle fibers were, however, vague.

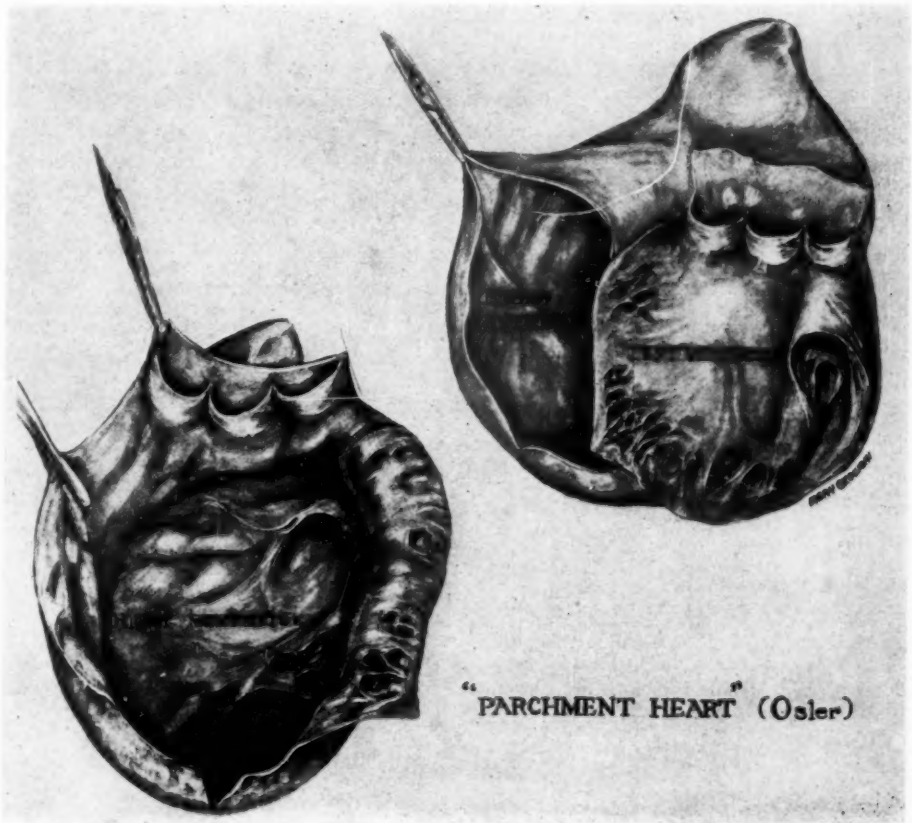

Fig. 1.—Two views of the heart with walls of parchment-like thinness; one view shows the interior of the right ventricle with the pulmonary artery and its valves and a portion of the tricuspid valve. Note the flat thin papillary muscle and the thin ventricular wall which in some parts consists of epicardium alone. The view which shows the interior of the left and part of the right ventricle demonstrates that the right is larger. Note fenestration of the aortic valve, and two arteriosclerotic plaques in the intima of the first portion of the aorta. Most of the auricular walls, and the ventricular walls in the vicinity of the cardiac apex, are transparent.

Osler recognized and pointed out the main remarkable feature of this heart: there is an extreme degree of dilatation without the hypertrophy that usually occurs. The absence of hypertrophy in this parchment-like heart poses the salient question about its pathogenesis. Starling's law of the heart may, in part, account for the dilatation, but it does not adequately explain the apparently long duration of life of the subject. Indeed, at present, no technique exists for reproducing such thin myocardium in an experimental animal. Among the various mechanisms that merit consideration, dystrophy of myocardium

in a person with generalised muscular dystrophy offers the possibility of an explanation. That the right auricle and ventricle are larger than the left suggests an element of cor pulmonale which may have been due to impairment in function of respiratory muscles.

It is very regrettable that this specimen is not accompanied by an adequate clinical history and autopsy protocol. Dr. Maude Abbott found it among a group of specimens donated to the Museum by Osler during his Montreal period, 1874 to 1884, and she included it in the special exhibit of Osler's contributions which she arranged in 1920. Dr. Abbott had no records belonging to it but recalled vaguely that this heart had been found in a man who had died suddenly while walking up a rather steep hill in Montreal. Osler visited the McGill Museum in February, 1905,[1] and may have seen the specimen on this occasion, for he first mentions it in the sixth edition of his book which appeared in that year.

Thus we are confronted with the fact, inherent in this specimen, that the myocardium may stretch to "parchment-like" thinness and continue to function. The etiology and the story of the evolution of this degree of dilatation can only be conjectured. Perhaps some form of general muscular dystrophy played the chief role in the processes which resulted in this condition. We know of no other similar case, nor of any experimental technique by which an analagous condition could be produced in animals. This specimen provides striking evidence in answer to the theoretical question, "How far can the process of dilatation of a human heart progress?"

REFERENCES

1. McDermott, H. E., and Abbott, Maude: A Memoir, Toronto, 1941, The Macmillan Company of Canada, Ltd., p. 90.
2. Osler, Wm.: The Principles and Practice of Medicine, ed. 6, New York, 1905, D. Appleton & Co., p. 820.

RIGHT-SIDED AORTIC ARCH

PHILIP SAMFT, M.D.,* AND DANIEL J. STONE, M.D.**

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THE medical literature has contained reports of aberrations in the development of the aortic arch or the arteries leading from it for a long time, but the first premortem diagnoses of such anomalies only date back less than thirty years.[1,2] With the development of new surgical techniques for the treatment of congenital heart disease, a great deal of interest has been aroused in detailed studies of aortic anomalies, both from the diagnostic and surgical viewpoints.[3-5]

Neuhauser[3] has developed a useful classification of aortic arch anomalies, especially with regard to right aortic arch without inversion of the heart itself. These have been divided into two groups. The first, or anterior, type is that in which the aortic arch is anterior to the trachea, with the descending aorta on the right side. The second, or posterior, type is that in which the aortic arch is retroesophageal, with the descending aorta coursing to the right of the normal descending aorta, but still descending on the left side. There is some disagreement in the literature as to whether the first or the second type is the more common. Mannheimer[6] and Garland[10] both claim that the right-sided descending aorta is the common type. Bedford and Parkinson[11] noted a right descending aorta in four of six noncardiac patients. On the other hand, Neuhauser[3] and Gross[7] both state that the anterior variety is rare, especially in normal hearts. It is their feeling that the anterior type is more common in transposition of the great vessels, while the posterior type is the rule in otherwise normal hearts.

Neuhauser[3] has further subdivided the posterior type, the left descending aorta type, into three groups. In the first there is a "right aortic arch in which the left subclavian artery arises last from the arch and crosses behind the esophagus." In the second there is a "right aortic arch in which no vessel arising from the arch crosses the mid-line posterior to the esophagus. A vessel may pass in front of the trachea." In the third type there is a "right aortic arch with a persistent left aortic diverticulum giving origin to the left subclavian artery." This case is being reported in order that evidence may be accumulated as to exactly what are the incidences of the various types of right aortic arch anomalies. In addition, the successful visualization of an aortic diverticulum (persistent left posterior aortic root) by angiocardiography is of interest.

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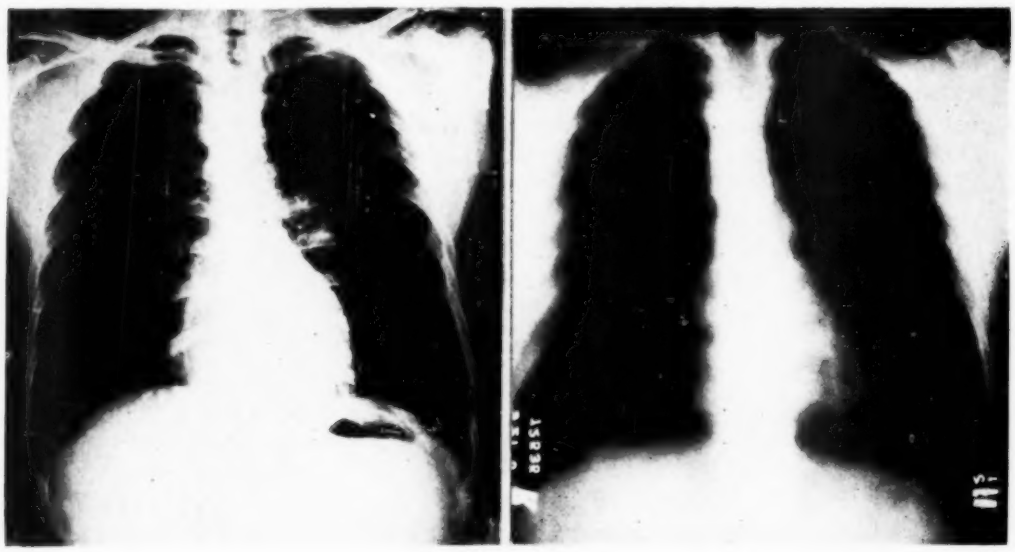
CASE REPORT

A. M. is a 44-year-old Puerto Rican man who was admitted to the hospital for status asthmaticus. His only complaints were related to the asthma of seven years duration. The heart was normal on physical examination. The admission chest film, Fig. 1,*A*, was interpreted as showing pulmonary emphysema. A bronchoscopy was done because of persistent small hemoptyses: compression of the trachea and distortion of the left main bronchus were noted. Tomograms were therefore obtained, and (Fig. 1,*B*) displacement of the trachea to the left was noted at the level of the aortic knob. A right aortic arch was therefore suggested as a diagnostic possibility. Esophagrams were therefore obtained (Fig. 2), and they confirmed this diagnosis. In the posteroanterior view (Fig. 2,*A*) there was a marked indentation on the right side of the esophagus at the level of



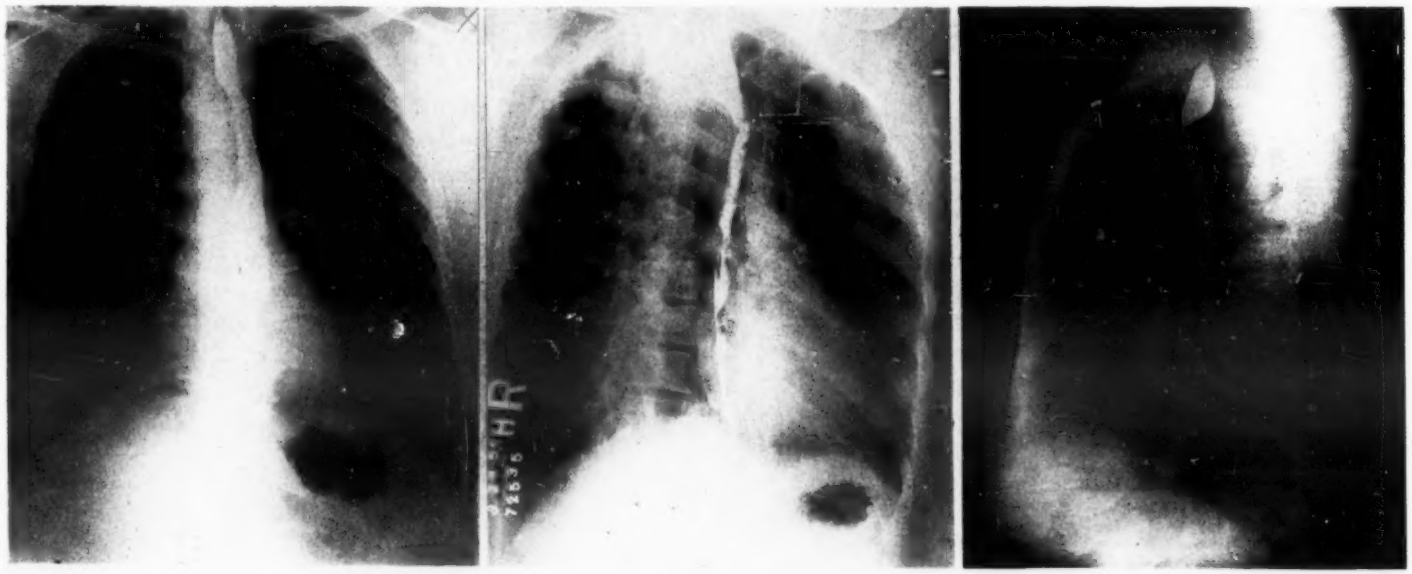
A. B.

Fig. 1.—*A*, Posteroanterior chest radiograph. Note the absence of an aortic knob in the usual site. *B*, Tomogram at a level of 11.5 cm. from the posterior chest wall. Note the aortic knob indenting the trachea on the right side.

the aortic arch. In the right oblique position (Fig. 2,*B*) the barium-filled esophagus was displaced forward at the level of the arch. Similar findings were noted in the left lateral position (Fig. 2,*C*). The marked indentation on the posterior wall of the esophagus in the latter two views raised the possibility of a right-sided aortic arch with a retroesophageal aorta and a subsequent left descending aorta. However, on fluoroscopy it was noted that the descending aorta was definitely on the right side. A left aortic diverticulum, a remnant of the posterior left aortic arch, was therefore postulated (Neuhauser[12]) to account for the posterior impression on the esophagus. Angiocardiography confirmed this thesis. Fig. 3,*A* shows the posteroanterior film with the radiopaque dye filling the ascending aorta, the right aortic arch, and the right-sided descending aorta. Fig. 3,*B* illustrates the left anterior oblique film, showing visualization of the ascending aorta, aortic arch, and the aortic diverticulum.

DISCUSSION

This case is of interest because of the incidental and accidental finding of a right aortic arch with a right descending aorta in a 44-year-old Puerto Rican man with bronchial asthma. The patient denied dysphagia at all times. The only complaints referable to either the cardiovascular or pulmonary systems were the dyspnea (which we felt was due to the bronchial asthma) and repeated small hemoptyses. The hemoptyses were ascribed to diffusely inflamed bronchial

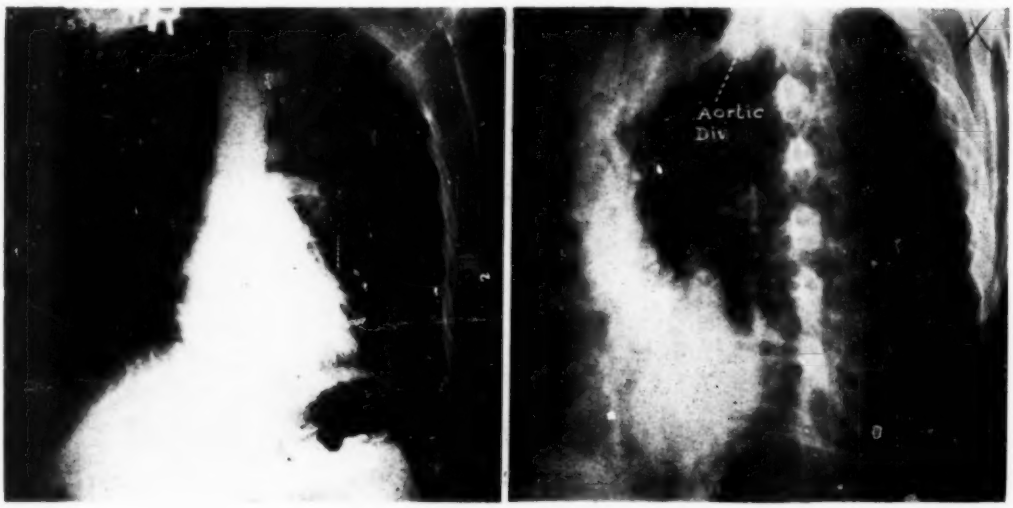


A. B. C.

Fig. 2.—*A*, Esophagram showing an indentation on the right side of the esophagus. *B*, Esophagram in the right anterior oblique position showing a forward displacement of the barium-filled viscus. *C*, Esophagram in the left lateral position showing the indentation in the barium-filled esophagus produced by the aortic diverticulum.

mucosa when bilateral bronchography and bronchoscopy revealed no other etiology for the hemoptysis.

Although the left subclavian artery was not visualized on angiocardiography, it is our thought that this vessel arose from the aortic diverticulum. According to Mannheimer,[6] the left subclavian artery rarely arises directly from the aortic arch when an aortic diverticulum is present; it usually arises from the diverticulum itself.



A. B.

Fig. 3.—*A*, Angiocardiogram showing filling of the ascending aorta, aortic arch, and right-sided descending aorta. *B*, Angiocardiogram in the left anterior oblique position showing filling of the aortic arch and diverticulum.

SUMMARY

A case of a right-sided aortic arch is presented with angiocardiographic confirmation of the exact type of right-sided arch present.

REFERENCES

1. Assmann, H.: Die Rontgendiagnostik der innerer Erkrankungen, ed. 3, Leipzig, 1924, F. C. W. Vogel, p. 103.
2. Arkin, A.: Totale Persistenz des rechten Aortenbogens im Rontgenbild, Wien. Arch. f. inn. Med. **12**:385, 1926.
3. Neuhauser, E. B. D.: The Roentgen Diagnosis of Double Aortic Arch and Other Anomalies of the Great Vessels, Am. J. Roentgenol. **56**:1, 1946.
4. Neuhauser, E. B. D.: Tracheo-Esophageal Constriction Produced by Right Aortic Arch and Left Ligamentum Arteriosum, Am. J. Roentgenol. **62**:493, 1949.
5. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, The Commonwealth Fund, p. 442.
6. Mannheimer, E.: Morbus Coeruleus, An Analysis of 114 Cases of Congenital Heart Disease With Cyanosis, New York, 1949, S. Karger, p. 58.
7. Gross, R. E., and Ware, P. F.: The Surgical Significance of Aortic Arch Anomalies, Surg., Gynec. & Obst. **83**:435, 1946.
8. Blalock, A.: Surgical Procedures Employed and Anatomical Variations Encountered in the Treatment of Congenital Pulmonic Stenosis, Surg., Gynec. & Obst. **87**:385, 1948.
9. Bahnson, H. T., and Blalock, A.: Aortic Vascular Rings Encountered in the Surgical Treatment of Congenital Pulmonic Stenosis, Ann. Surg. **131**:356, 1950.
10. Garland, L. H.: Persistent Right-Sided Aortic Arch, Am. J. Roentgenol. **39**:713, 1938.
11. Bedford, D. E., and Parkinson, J.: Right Sided Aortic Arch (Situs inversus arcus aortae), Brit. J. Radiol. **9**:776, 1936.
12. Neuhauser, E. B. D.: Medical Progress: Recent Advances in the Roentgenographic Diagnosis of Congenital Malformation of the Heart and Great Vessels, New England J. Med. **242**:753, 1950.

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